Neurology

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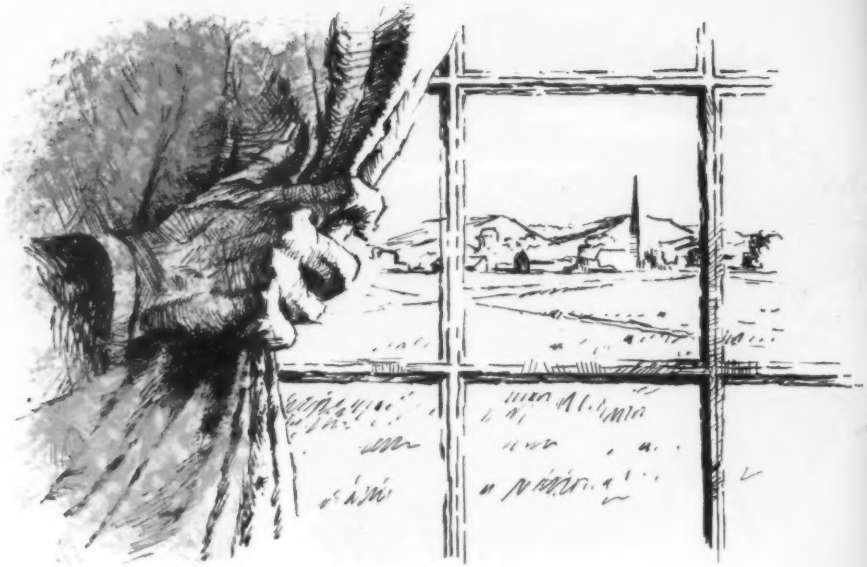

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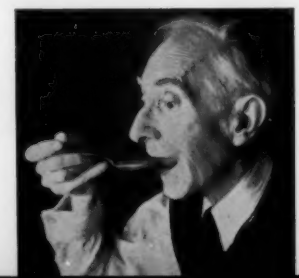

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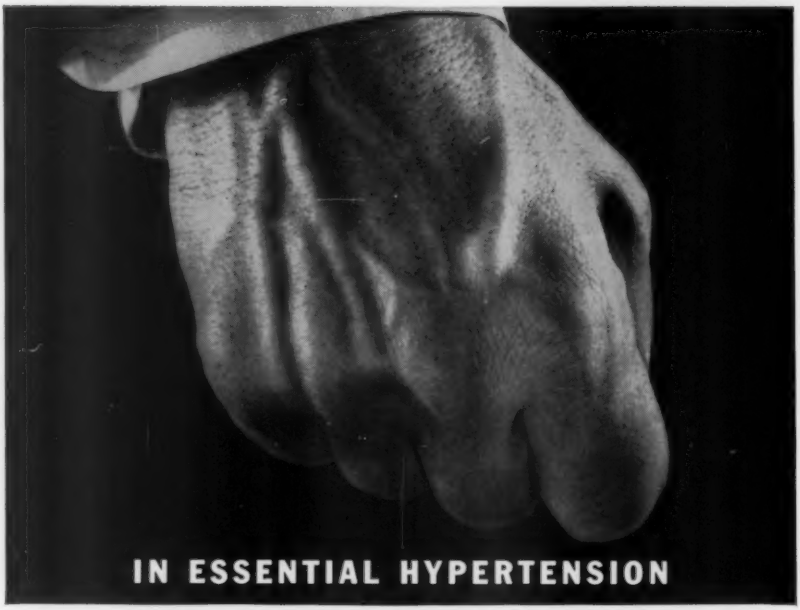

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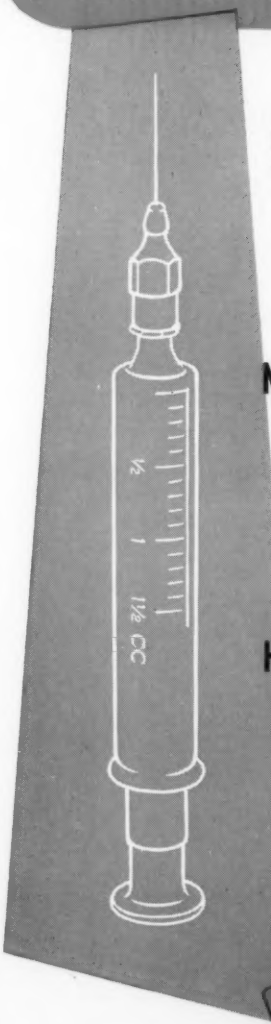

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INFORMATION FOR *Authors*

NEUROLOGY, the official publication of the American Academy of Neurology, has been instituted to provide a medium for prompt publication of articles dealing with neurology and its cognate fields and to stimulate individual investigation in these various fields.

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Neurology

Spontaneous Occlusion of the Internal Carotid Artery

Emanuel H. Feiring, M.D.

SINCE the introduction of cerebral angiography and its subsequent widespread utilization as a diagnostic method, the occurrence of spontaneous occlusion of the internal carotid artery has become increasingly evident. In 1937 Moniz and his co-workers[27] described the first four cases in which the diagnosis had been established by arteriography. Fourteen years later, in 1951, when Johnson and Walker[20] published their collective review, they were able to assemble 101 cases from the literature (two involved the common carotid arteries), in addition to which they reported six of their own. Since then the number of cases reported has been augmented still further. Publications by Elvidge and Werner,[13] Shapiro,[31] Gross,[17] Denny-Brown,[10] Poppen and Baird,[30] Askenasy and Wijsenbeek,[4] Bonnal and co-workers,[7] Müller,[28] Bertrand and Léger,[6] Gurdjian and Webster,[18] and others have recently appeared in which a substantial number of additional cases have been described.

It is apparent that, although only relatively recently recognized as a clinical entity, this condition is actually not at all uncommon. According to Lima,[22] occlusive disease of the internal carotid artery was observed in Moniz's clinic in about one per cent of all patients subjected to arteriography. He further stated that this figure would probably be much greater were all patients with hemiplegia similarly investigated.

From the neurosurgical services of the Beth Israel and Mount Sinai Hospitals, New York City.

Presented at the combined meeting of the Philadelphia Neurological Society, the New York Neurological Society, and the Section of Neurology and Psychiatry of the New York Academy of Medicine, April 17, 1953.

AUTHOR'S MATERIAL

In the course of performing an estimated 500 angiograms on patients suspected primarily of harboring intracranial tumors or vascular anomalies, seven cases of spontaneous occlusion of the internal carotid artery were encountered. On the basis of the clinical evidence alone, before angiography, a neoplasm was diagnosed in all but two. It is perhaps appropriate at this point to mention that the four cases which provided the basis of the original report by Moniz and his associates[27] had also been regarded as probable tumors on clinical grounds. According to Milletti,[25] a space-occupying lesion so often enters into a differential diagnosis that most patients suffering from thrombosis of the internal carotid artery are referred to the neurosurgeon with a diagnosis of brain tumor. The majority of the 107 cases reviewed by Johnson and Walker had been considered probable neoplasms or aneurysms prior to arteriography.

Case 1.—Progressively developing hemianopsia, hemiparesis, and aphasia in a 63 year old male. Occlusion of internal carotid artery demonstrated by means of angiography. Pneumoencephalographic evidence of cerebral atrophy. Focal electroencephalographic abnormality. Death. Duration of illness seven months.

History. A 63 year old right-handed needle trade worker was referred on April 17, 1950, because of impairment of speech and weakness of the right side. About seven weeks previously he became aware of a visual defect and consulted an ophthalmologist, who discovered a right homonymous hemianopsia. Soon thereafter other symptoms appeared. On leaving home he became confused and unable to find his way about the city. About the same time abnormal speech was noted. He would start talking, but after saying a few words was unable to continue. Awareness of these shortcomings left him considerably depressed. Approximately one month after the onset of symptoms his right hand was noted to be weak. It was learned that from time to time over a period of many years he was unable to extend the fingers of this hand upon awakening. Within a few minutes full use of this part could be recovered. On this occasion, however, the weakness did not subside, but became more pronounced and spread to involve more proximal parts of the extremity and finally the face as well. His speech deteriorated further and was finally reduced to a few monosyllabic words.

Physical examination. The patient exhibited a pronounced aphasia, mainly expressive in nature. Verbal commands were carried out quite well. A right homonymous hemianopsia was demonstrable by gross confrontation. A right hemiparesis was present, affecting the face and upper extremity severely. The deep tendon reflexes were increased in the right upper limb. Both plantar responses were flexor. The optic disks were clearly outlined and flat. Pinprick appreciation appeared to be intact throughout. It was difficult to test other forms of sensation. Blood pressure was 136/86.

Laboratory data. The blood count and urinalysis were negative. Roentgenograms of the chest and skull disclosed no abnormalities. The pineal gland was calcified and by measurement was in its normal position. An electroencephalogram revealed a moderate amount of two to four per second high amplitude waves over the entire left hemisphere, most marked in the parietal and occipital regions, and depressed alpha activity on that side.

Course. A neoplasm of the left cerebrum was suspected and an arteriogram performed on that side. Injection of the common carotid artery resulted in visualization only of the branches of the external carotid artery (figure 1). The internal carotid artery appeared to be occluded at its origin. A lumbar pneumoencephalogram disclosed moderate enlargement of the ventricles and considerable dilatation of the subarachnoid spaces indicative of cerebral atrophy (figure 2). The cerebrospinal fluid protein was 37.7 mg. per cent.

Following discharge from the hospital in May 1950, power in the right upper extremity

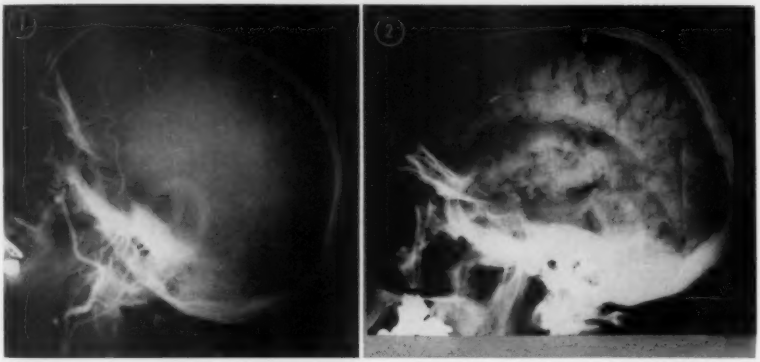

FIG. 1. *Case 1.* Occlusion of internal carotid artery at its origin. Only external carotid circulation is visible.

FIG. 2. *Case 1.* Ventricular dilatation and widening of subarachnoid sulci.

improved considerably, but speech remained severely affected. In July 1951, he exhibited evidence of a left homonymous hemianopsia. Thereafter he deteriorated rapidly and died on September 13, 1951.

Case 2. Insidious onset of dysfunction of hand, followed by apoplectiform hemiparesis and still later by unilateral amaurosis in a 51 year old male. Focal electroencephalographic abnormality. Occlusion of internal carotid artery revealed by angiography. Normal pneumoencephalogram. Improved sufficiently to resume work.

History. A 51 year old right-handed draftsman was admitted to the hospital on April 6, 1950, because of defective vision in the right eye and weakness of the left side of the body. He was well until the beginning of February 1950, when he began to experience intermittent pain in the left upper extremity and awkwardness in the use of that hand. These symptoms were attributed to cervical hypertrophic osteoarthritis. About a month later he suddenly developed numbness and weakness of the left upper and lower extremities. The paralysis was maximal at onset and receded gradually. Four days prior to hospital admission he suddenly became aware of defective vision in the right eye and an accentuation of the left-sided weakness. The left side of the face was also involved on this occasion. These symptoms were accompanied by a severe headache.

His past history included several episodes of chest pain, thought to have been due to coronary insufficiency, and burning sensations in the tips of the fingers and toes during the previous two years, for which a vascular etiology had been suggested.

Physical examination. The patient exhibited a spastic left hemiparesis with increased deep tendon reflexes, knee and ankle clonus, a positive Hoffmann sign, and an equivocal plantar response on that side. Pinprick and touch were perceived less acutely on the affected side and position sense was impaired in the toes of the left foot. Stereognosis was defective in the left hand. Vibratory appreciation was preserved throughout. He was totally blind in the right eye and the pupil on that side failed to react to light. The response to consensual stimulation, however, was preserved. On the right side the fundus disclosed a pale and edematous retina with blurred disk margins. Blood vessel changes were pronounced. The arteries were attenuated, often wire-like, and segmented, and the veins were thin and collapsed. A small cherry-red spot was present in the region of the macula. These findings were interpreted as indicative of a thrombosis of the cerebral artery of the retina, an opinion substantiated by an ophthalmologic colleague. Blood pressure was 130/95.

Laboratory data. A blood count and urinalysis disclosed no abnormalities. The fasting blood sugar was 112 mg. per cent and the nonprotein nitrogen level 35 mg. per cent. Both blood and cerebrospinal fluid serology were negative. An electrocardiogram revealed a left axis deviation. Roentgenograms of the skull and chest were not unusual. An electroencephalogram disclosed a slower alpha activity and low to moderate voltage three to six per second waves over the right hemisphere, most marked in the frontal and temporal regions.

Course. Vascular disease was suspected and a right cerebral angiogram performed. The common carotid artery was injected with Diodrast, but only the external carotid circulation was visualized. A second injection yielded similar results. An occlusion of the internal carotid artery at its origin was diagnosed. Pneumoencephalography disclosed a normal ventricular system without displacement or deformity.

On April 12, 1950, the patient developed a thrombophlebitis of the left lower extremity. This gradually improved following ligation of the femoral vein.

When last heard from in March 1953, he complained of numbness of the left side of the body and defective vision in the right eye. He was doing a full day's work and driving an automobile on weekends.

Case 3.—Progressive hemiparesis and alexia affecting a 49 year old male. Focal electroencephalographic changes. Angiographic demonstration of occlusion of internal carotid artery. Considerable cerebral atrophy visible in the pneumoencephalogram. No improvement.

History. A 49 year old right-handed male bookkeeper was referred on March 8, 1950, because of impairment of function of the extremities on the right and inability to read. He was a Jewish refugee who had been imprisoned in a Nazi concentration camp and subjected to considerable maltreatment. His symptoms began in 1945, soon after learning that his entire family had been exterminated in a crematorium. At that time he became aware of a lack of sensation in the thumb and forefinger of the right hand. The numbness spread to involve the arm, and about a year later the lower extremity was affected similarly. Thereafter his ability to read and write became progressively impaired. He was finally unable to read even his daily prayer, though able to recite it perfectly from memory. Other symptoms referable to his nervous system, including headache, convulsions, and visual disturbances, were denied. His past history was not otherwise significant.

Physical examination. The pertinent findings included a spastic right hemiparesis with increased deep tendon reflexes and a positive Babinski sign on that side, and an alexia. He was able to understand and speak Hebrew and German quite well. Except for the right central facial weakness, examination of the cranial nerves disclosed no abnormalities. The fundi appeared normal and by gross testing, there was no evidence of a visual field defect. Sensation was intact. Blood pressure was 190/118.

Laboratory data. A blood count showed 15,150 white cells per cu. mm., 80 per cent of which were polymorphonuclear leukocytes. Urinalysis was negative. The fasting blood sugar was 106 mg. per cent. Bilateral apical fibrosis was demonstrable in the roentgenograms of the chest. The heart shadow was enlarged in its transverse diameter. Roentgenograms of the skull disclosed slight atrophy of the posterior clinoids and a hyperostosis of the inner table in the left frontoparietal parasagittal region, suggestive of a meningioma. Electroencephalography revealed a slow alpha rhythm in the left temporal region and a small to moderate amount of sporadic and serial one to three per second activity in the same area.

Course. In view of the clinical picture and the roentgenographic changes in the skull, the possibility of a meningioma was considered. Accordingly a left carotid arteriogram was performed. The common carotid artery was injected with Diodrast, but only the external carotid circulation was visualized (figure 3). A similar picture was obtained after a second injection. Based on the angiograms, occlusive disease of the internal carotid artery was diagnosed. In order to demonstrate the amount of anticipated cerebral atrophy, air

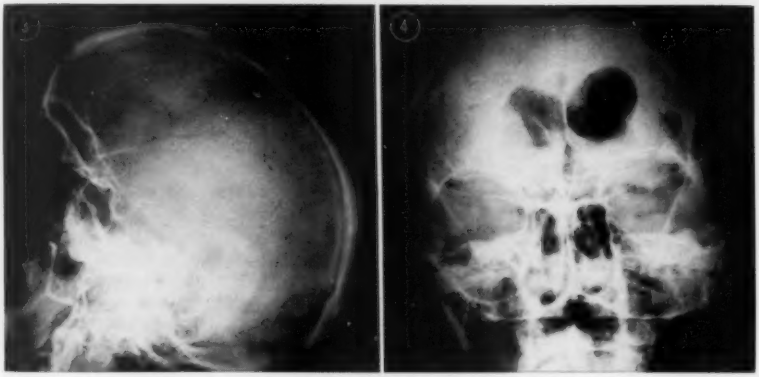

FIG. 3. *Case 3.* Only branches of the external carotid artery are demonstrable.

FIG. 4. *Case 3.* Considerable asymmetric dilatation of the ventricles. The ventricle on the affected side is larger.

studies were done. A considerable degree of ventricular dilatation was seen, the left lateral ventricle being appreciably larger than the right. There was no displacement or deformity. The cerebral sulci appeared widened (figure 4). These findings indicated the presence of considerable cerebral atrophy affecting especially the left hemisphere. The cerebrospinal fluid protein was 33 mg. per cent. No change has occurred in this patient's condition.

Case 4.—Focal seizures, weakness, and speech impairment affecting a 62 year old male. Bitemporal electroencephalographic abnormality. Occlusion of internal carotid artery diagnosed by angiography. Moderate degree of cerebral atrophy. Improvement.

History. A 62 year old right-handed salesman sought advice on March 20, 1952, because of impairment of speech and weakness of the extremities on the right side. His symptoms began 27 months previously when he lost consciousness for an estimated period of ten to 15 seconds while driving his car. Fortunately he was able to park the car before coma supervened. He consulted a physician who found he was suffering from hypertension and diabetes and prescribed dietary treatment. In June 1950, he suddenly developed a seizure of the right hand which lasted about a minute. This subsequently recurred and was followed by transient weakness of that limb of a few minutes' duration. Later that year he began to experience seizures involving the right lower extremity. These did not occur in association with or follow a convulsion of the upper limb. At no time did loss of consciousness accompany a seizure. In November 1950, he was unable to speak for about a minute on one occasion. About this time weakness of the right upper extremity also became manifest. About March 1951, it was noted that his speech had become slow and his writing impaired. Since February 1952, he was aware of difficulty in finding words to express himself. Early in March 1952, he began to drag the right lower extremity. At no time did he complain of headache.

Physical examination. The patient was fully oriented, alert, and cooperative. Some minor memory defects were demonstrable. No definite impairment of speech could be detected. He was invariably able to name test objects correctly; even complex commands were properly executed. Calculations were readily performed without error. The right side of the face appeared slightly flattened, but otherwise the cranial nerves were intact. There was no evidence of papilledema, and the visual fields were normal. Weakness was limited to the right lower extremity. Movements at the ankle were considerably impaired, the

Barré test was positive, and he circumducted the limb when walking. The deep tendon reflexes were more active on the right side, and a right Babinski toe sign was elicited. The abdominal reflexes on the right side were absent. All modalities of sensation, including stereognosis and double simultaneous stimulation, were intact. Blood pressure was 150/90.

Laboratory data. Routine blood and urine studies revealed no abnormality. The fasting blood sugar was 95 mg. per cent. An electrocardiogram showed a left axis deviation. Roentgenograms of the chest and skull were negative. An electroencephalogram disclosed a slight alternating asymmetry of alpha frequency and a small amount of low to moderate voltage sporadic delta activity over both temporal regions. No focal concentration of radioactive diiodofluorescein was demonstrable.

Course. A left cerebral tumor was suspected and an angiogram performed on that side. The common carotid artery was injected with Diodrast, but only the external carotid artery and its branches were visualized. It was therefore concluded that the internal carotid artery was obstructed, in all probability as a result of a thrombosis. To determine the extent of cerebral atrophy, a pneumoencephalogram was performed. Widening of the subarachnoid spaces, indicative of a moderate amount of cortical atrophy, was observed. There was no displacement or deformity of the ventricular system. The protein content of the cerebrospinal fluid was 42 mg. per cent. Anticoagulant therapy was instituted.

In the year that has elapsed since his discharge from the hospital, he has improved considerably and resumed his occupation. Weakness of the lower extremity has almost entirely disappeared, and according to his family his speech is distinctly better. The deep tendon reflexes remain more active on the right and an extensor plantar response is still demonstrable on that side. Since his blood pressure had risen appreciably, the use of dicoumarol has been discontinued.

Case 5.—Episodic aphasia and hemiparesis of transient duration affecting a 55 year old male. Subsequent persistent aphasia and organic mental syndrome. Focal electroencephalographic abnormality. Arteriographic demonstration of occlusion of internal carotid artery. Evidence of cerebral atrophy. Death resulting from coronary occlusion.

History. A 55 year old right-handed motion picture projectionist was referred on March 26, 1952, because of defective memory, impairment of speech, disturbance of function of the right half of the body, and a feeling of stiffness of the left side of the face. About three or four years previously he had experienced an episode of double vision attributed by a physician to a diseased blood vessel. He wore a shield over one eye for four or five weeks, after which the diplopia disappeared. It was difficult to be sure but he thought the left eye was the one involved. Approximately two years later while listening to the radio, he developed severe headache, vomiting, and vertigo. These symptoms were associated with inability to walk due to a loss of balance. He recovered after a period of about five weeks and was told by a physician that he had suffered a hemorrhage in "the back of the head." Soon thereafter he began to experience episodes of inability to speak, accompanied by weakness of the limbs on the right side. These lasted for ten to 15 minutes, were not associated with convulsions, and recurred at intervals varying from days to weeks. In November 1951 examination revealed a nominal aphasic defect and slight weakness of the right side of the face and of the right upper extremity. On February 10, 1952, a disturbance of speech again became manifest and he lost both power and the ability to perceive sensation on the right side. Following this attack, weakness in the right upper extremity persisted though the lower limb recovered. Two weeks later he suddenly became unconscious for a period of about a minute. On regaining consciousness he exhibited a mixed aphasia and a right facial paresis.

Evidence of peripheral vascular disease was manifested by coldness of the lower extremities, blanching of the feet on elevation, absence of pulsations of the dorsalis pedis and posterior tibial arteries, and calcification visible in the roentgenograms. An elevated fast-

ing blood sugar and electrocardiographic evidence of a mild degree of myocardial ischemia were additional significant findings.

An electroencephalogram in November 1951 revealed a small amount of sporadic, low voltage, two to six per second activity over the left temporal region. Lumbar puncture also done at that time disclosed clear cerebrospinal fluid under a pressure of 100 mm. of water and containing 59.4 mg. per cent protein. Roentgenograms of the skull were reported negative.

Physical examination. The patient was disoriented and his memory was grossly defective. Thus he was unable to recall his address or telephone number. A pronounced degree of aphasia, essentially nominal in type, was evident. Frequently, when the name of an object was requested of him, he was unable to reply in English but did so, usually correctly, in German. It should be stated that he had lived in this country many years and had learned to speak English well. Verbal commands, even complicated ones, were executed correctly. Right and left differentiation was intact. On testing his capacity to calculate, he initiated the 100 minus 7 test correctly, but thereafter was unable to continue.

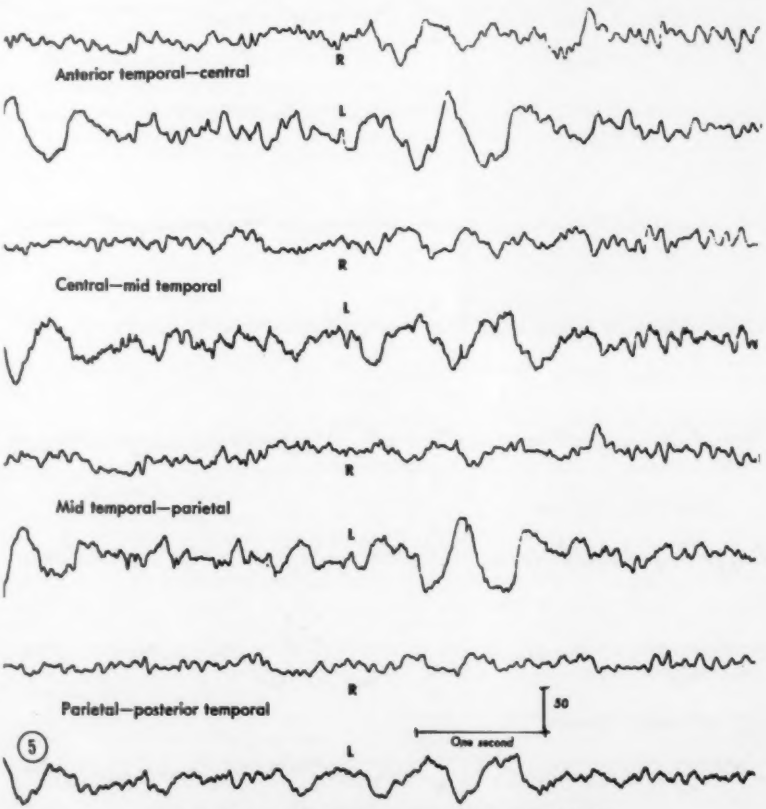

FIG. 5. *Case 5.* Prominent slow wave activity on the left side.

The cranial nerves were intact except for a right facial flattening. Funduscopic examination disclosed clearly outlined optic disks; the retinal vessels appeared sclerotic. There was no demonstrable weakness of the extremities and gait was normal. The deep tendon reflexes were about equally active on the two sides. The plantar responses were both flexor. Neither abdominal reflexes were elicited. All modalities of sensation, including stereognosis, were preserved. Some degree of apraxia involving the right hand was demonstrable. By gross confrontation the visual fields were full. Blood pressure measured 140/70.

Laboratory data. The blood count and urinalysis were normal. The fasting blood sugar level was 172 mg. per cent. Roentgenograms of the chest and skull revealed no abnormalities. The pineal shadow was not displaced. Electroencephalography disclosed a large amount of high voltage sporadic, serial and paroxysmal one to two per second activity on the left side, maximal in the frontotemporal region (figure 5). Injection of Diodrast into the left common carotid artery resulted in visualization only of the branches of the external carotid artery. A pneumoencephalogram demonstrated symmetrical ven-

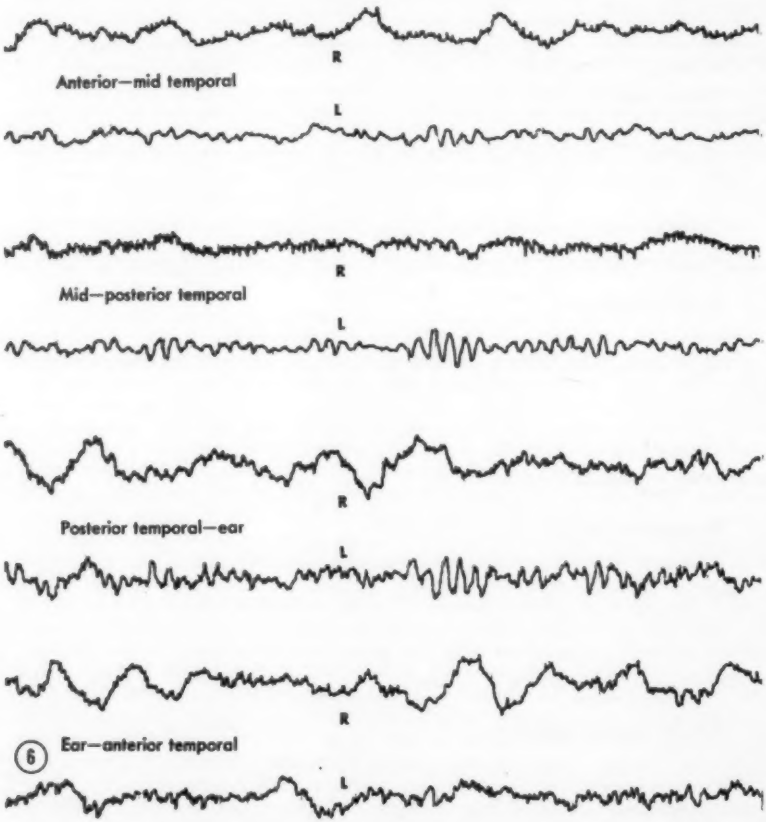

FIG. 6. *Case 6.* Diminished alpha activity, together with slow waves present on the right side.

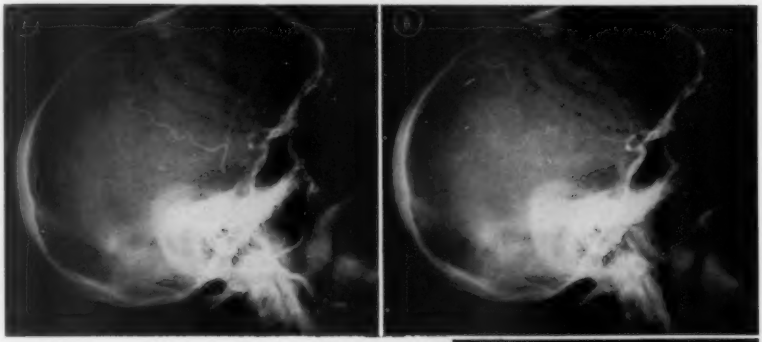

FIG. 7. *Case 6.* Delayed filling of internal carotid circulation. Compare with figure 1, case 2 of List and Hodges.[22]

FIG. 8. *Case 6.* Dye is present only in the branches of the middle cerebral artery. These appear narrowed and reduced in number.

FIG. 9. *Case 6.* Slight enlargement of the ventricles and dilatation of the subarachnoid spaces.

tricular dilatation without displacement or deformity. The sulci of both hemispheres were visualized and appeared widened, particularly on the left side.

Subsequent course. Anticoagulant therapy was administered, but had to be discontinued because of bleeding. Death occurred as a result of a coronary occlusion in July 1952.

Case 6.—Two episodes of hemiparesis occurring in a 57 year old male. Focal electroencephalographic abnormality. Angiographic evidence of partial occlusion of internal carotid artery intracranially. Demonstrable cerebral atrophy. Persistent organic mental syndrome necessitating hospitalization.

History. A 57 year old right-handed plumber was admitted to the hospital on September 26, 1950, because of weakness of the left side of the body. Approximately two months prior to admission he suddenly developed a left-sided paralysis which disappeared within a few hours. Some time thereafter he suffered a recurrence which left him with a residual weakness. Since the onset of his illness he had experienced intermittent headaches. There were no other symptoms referable to the nervous system and his past history was not remarkable.

Physical examination. The patient was oriented but memory impairment was clearly evident. Calculations were performed with difficulty. He displayed a left hemiparesis, most pronounced in the lower extremity, with increased deep tendon reflexes and a positive Babinski sign on that side. All modalities of sensation were defective on the left. Except for the facial weakness, examination of the cranial nerves disclosed no abnormalities. The fundi were entirely normal. Blood pressure measured 118/74.

Laboratory data. A blood count and urinalysis were negative. The fasting blood sugar was 109 mg. per cent. The blood and cerebrospinal fluid Wassermann reactions were negative. Roentgenograms of the chest and skull disclosed no abnormalities. Electroencephalography revealed a marked decrease of alpha activity on the right side and moderate to high voltage, sporadic and serial, one to three per second waves in the right frontotemporal region (figure 6).

Course. In view of the severe focal electroencephalographic abnormality, the possibility of a tumor was considered and a right carotid arteriogram performed. Following an injection of Diodrast into the common carotid artery, visualization of the external carotid circulation preceded that of the intracranial vessels (figure 7). Only branches belonging to the middle cerebral group were seen and these were unusually narrow and relatively few in number (figure 8). These findings were interpreted as indicative of a partial occlusion of the intracranial portion of the internal carotid artery. Pneumoencephalography revealed evidence of cerebral atrophy. The ventricles were slightly enlarged but neither displaced nor deformed. The cerebral sulci were distinctly widened (figure 9). The cerebrospinal fluid protein content was 51 mg. per cent.

When examined again in October 1951, he had recovered considerable strength on the affected side. Though the plantar response on the left was now flexor, the deep tendon reflexes were still hyperactive and sensation remained impaired. His memory was defective, his judgment poor, and he expressed many paranoid ideas. He was subsequently admitted to a mental hospital.

Case 7.—Transient hemiparesis, followed by a temporary contralateral amaurosis in a 48 year old male. Persistent sensory deficit. Pneumoencephalographic evidence of cerebral atrophy. Intracranial occlusion of internal carotid artery demonstrated angiographically. Condition unchanged.

History. A 48 year old right-handed sanitation truck driver was first seen on September 12, 1951, because of a feeling of numbness in the left hand. His illness was initiated by what he described as an involuntary movement of the left upper extremity on December 21, 1950. About a week later this limb suddenly felt numb and stiffened. Immediately thereafter he apparently lost consciousness for an estimated period of 15 or 20 minutes. He was not incontinent during this time, nor did he bite his tongue. On recovering consciousness he was unable to move the upper or lower extremities on the left side. The weakness was only of transient duration, but a residual numbness of the left upper extremity persisted. In January 1951 he became aware of blurred vision in the right eye on awakening one morning. This was not associated with any pain. After an unspecified period of time normal vision was regained. Examination on April 18, 1951 disclosed considerable emotional lability, astereognosis of the left hand, and hypesthesia and hypalgesia on the left side, involving the face, upper extremity, and upper trunk. An electroencephalogram performed at the same time revealed no abnormality. Lumbar puncture disclosed clear cerebrospinal fluid under a pressure of 190 mm. water, and containing 70 mg. per cent protein and one white cell per cu. mm. There were no further episodes of weakness or loss of consciousness, but the patient continued to complain of numbness of the left hand. He was able to grasp objects securely with that hand but was unable to feel what he was holding. Except for an occasional headache, other neurologic symptoms were denied. His past history was irrelevant.

Physical examination. There were no abnormalities referable to the cranial nerves. The appearance of the optic disks was not unusual. Motor power in the limbs was intact and the deep and superficial reflexes equally active on the two sides. There were no pathologic reflexes. Pinprick was said to be felt less well over the entire left half of the body. The left side of the face and the left upper extremity were also less sensitive to touch. Position sense was impaired in the fingers of the left hand. He was unable to perceive objects placed in that hand. Two-point discrimination was also defective. Vibratory appreciation was preserved. Blood pressure was 120/80.

Laboratory data. The blood count was normal. Urinalysis revealed a trace of albumin. The fasting blood sugar was 145 mg. per cent. Roentgenograms of the skull and chest were negative. A normal electroencephalogram was recorded. Routine perimetric and tangent screen studies disclosed intact visual fields. However, using a 4 mm. green test object at a distance of 2 meters, a central defect was demonstrated on the right side. Visual acuity was 20/20 on both sides.

Course. The significance of the visual symptomatology was not appreciated at first and the possibility of a right cerebral neoplasm was entertained. Accordingly a pneumoencephalogram was performed. The ventricular system was displaced slightly from left to right but no deformity was observed. The third ventricle was slightly enlarged. Dilatation of the subarachnoid sulci was present, indicating cortical atrophy. This was especially evident in the region of the island of Reil on the right side. The cerebrospinal fluid protein content was 86 mg. per cent. The possibility of an occlusion of the internal carotid artery was suspected at this stage and cerebral angiography was undertaken. Diodrast was injected into the right common carotid artery after exposing the vessel surgically. Branches of the external carotid artery were promptly demonstrated by the dye. Visualization of the internal carotid artery, however, was delayed and imperfect. Only a narrowed segment of the vessel was seen in the parasellar region below and above the level of the clinoid processes. The major branches of the internal carotid artery were not visualized. A second injection of Diodrast into the common carotid artery yielded similar results. The angiograms were interpreted as indicative of an occlusion of the intracranial portion of the internal carotid artery.

No change has occurred in this patient's condition.

All seven patients were males, their ages at the time they came under observation varying from 48 to 63 years. The mean age was 55 years. The shortest duration of symptoms was two months, the longest five years. A progressive course characterized the clinical symptomatology in four cases. In the other three cases episodic manifestations occurred, such as weakness, aphasia, and loss of consciousness, frequently of transient duration.

Evidence of associated peripheral or cardiovascular disease was demonstrable in four patients: two had hypertension and two diabetes. The left side was involved in four cases, the right in three. Seizures, focal in nature, occurred in two patients. Headache was a prominent feature in only two instances. A hemiparesis was either evident at the time of examination or had been present some time during the course of the disease in every case. In one patient it represented a transient postconvulsive phenomenon. Aphasic manifestations occurred in all four patients with lesions affecting the dominant hemisphere. Evidence of an organic mental syndrome of varying severity was noted in four cases. Sensory disturbances were detected in three of the six patients whose responses were sufficiently reliable for evaluation. An homonymous hemianopsia was found in only one case. Permanent monocular amaurosis developing suddenly on the side of the carotid occlusion was observed in one patient, while transient homolateral blurring of vision was reported by another. In the former case the funduscopic appearance was that of a closure of the central retinal artery. The cerebrospinal fluid protein content varied between 33 and 86 mg. per cent.

A normal electroencephalogram was observed in only one case. A slight alternating asymmetry of alpha frequency and a small amount of low to

moderate voltage sporadic delta activity over both temporal regions was recorded in another case. In the remaining five patients there was slowing of the alpha, with some amplitude asymmetry, either higher or lower, and fairly diffuse delta activity, usually with focal accentuations at the frontal and temporal electrodes, all on the affected side.

Occlusion of the artery occurred in the neck beyond the bifurcation of the common carotid artery in five cases. In the remaining two cases, in one of which only a partial obstruction appeared to be present, the lesion affected the intracranial component of the vessel.

Anatomic verification of the lesion was not obtained in any patient in this series. Radiographic criteria for the diagnosis, therefore, are very important. The contrast medium was injected into the common carotid artery and, in those instances in which the obstruction occurred in the neck, only the external carotid circulation was visualized. In one case in which the occlusion was incomplete, visualization of the internal carotid circulation was delayed and the vessels reduced in caliber. In each instance the injections of Diodrast were repeated and the observations confirmed. Angiography of the uninvolved side was not performed since the injection of Diodrast into the contralateral patent carotid artery of such patients is dangerous and fatalities have been reported.[4,20].

All patients were subjected to pneumoencephalography. In six, symmetrically dilated ventricles and/or widened subarachnoid spaces were demonstrated. The pneumoencephalogram in one case was entirely normal.

Definitive therapy was attempted in only two patients, both of whom were given dicoumarol. It was discontinued in one patient soon after treatment was begun because of the occurrence of hemorrhagic phenomena, and in the other patient after about a year when his blood pressure rose considerably. The former patient has since died of a coronary occlusion, while the latter has improved appreciably and resumed his occupation. Of the remaining five untreated cases, one is psychotic and confined to a mental institution, one is a chronic invalid, another remains unimproved though not severely handicapped, one died presumably of progressive cerebral vascular disease, and one has improved sufficiently to return to work.

DISCUSSION

These observations for the most part conform to the recorded descriptions of the symptomatology and course of thrombosis of the internal carotid artery. As indicated by Moniz[26] and by others, this condition mainly affects adult males, reaching its highest incidence among those in the fifth and sixth decades of life. Its mode of development is quite variable. Based on the data compiled by Johnson and Walker,[20] hemiplegia of abrupt onset associated often with a loss of consciousness occurs in about 35 per cent of cases. A slow progressive course marked by contralateral weakness, sensory loss, hemianopsia, aphasia, headache, mental impairment, and occasionally convulsions is observed in about 25 per cent of patients. The remaining 40 per cent

exhibit a clinical picture characterized by transient episodes of headaches, hemiparesis or monoparesis (upper limb), aphasia, or sensory disturbances, which eventually may not clear entirely or may be catastrophically terminated by a sudden hemiplegia.

With regard to ocular symptomatology, of the 107 cases analyzed by Johnson and Walker,[20] episodes of transient blindness occurred in five, optic atrophy with visual loss in 11, and a homonymous hemianopsia in 12. Pupillary abnormalities, ptosis, papilledema, and diplopia were reported in a few cases. Transient monocular blindness occurred in six cases reported by Fisher.[15] He further indicated that the episodes of amaurosis usually cease following the advent of a contralateral hemiplegia. Two instances of homolateral blindness and loss of the contralateral temporal field were observed by Walsh and Smith.[35] These authors also noted that in this condition, the homonymous field defect may be transient and that the upper quadrants tend to be spared. A "tonometric retinal syndrome," characterized by a lower systolic retinal pressure on the side of the lesion and a bilateral decrease of retinal arterial pressure following compression of the carotid artery on the uninvolved side, was described by Milletti.[25] According to Denny-Brown,[11] narrowing of the retinal vessels on the side of the lesion may be observed following compression of the opposite carotid artery or pressure on the globe of the eye in about half the cases.

Clinical and electroencephalographic changes following compression of the uninvolved carotid artery have been reported.[7,10] Denny-Brown observed a discharge of slow waves and later spikes in the frontoparietal region of the normal hemisphere, together with an associated head movement. Diminution or absence of carotid pulsation in the neck has been reported by a number of observers. Dunning[12] recently described three cases in which pharyngeal palpation failed to reveal carotid pulsation on the affected side.

As might be anticipated, pneumoencephalography has usually disclosed evidence of cerebral atrophy. Gas studies performed in almost one-half of the cases reviewed by Johnson and Walker[20] as a rule revealed dilatation of the ventricles, often more marked on the side of the lesion. Enlargement of the subarachnoid spaces was also noted frequently. Similar findings have been described in subsequent reports. Occasionally the pneumoencephalograms have been entirely normal.

Concerning the electroencephalographic pattern in this condition, Ameli and Ashby[1] reported considerable abnormality on the involved side with focal accentuation in the posterior parietal region in one of their cases. Barré, Rohmer, and Isch[5] observed slow wave foci of increased voltage in the central and temporal regions of three patients. More complex changes, including a focus of diminished alpha frequency and voltage in the parietal zone, increased alpha amplitude in the temporal and occipital areas with superimposed theta activity were described in a fourth case. A normal record was reported by Johnson and Walker[20] in three of the four cases in which electroencephalography was performed. "Slowing with absence of the alpha

rhythm" on the side of the lesion was described in their fourth case. Delta waves of varying amplitude localized to the frontotemporal region of the affected side were observed in five cases by Elvidge and Werner.[13] In an additional two cases, the electroencephalogram showed evidence of generalized cerebral dysfunction in one and abnormal slow waves and depression of alpha rhythm in another. A normal electroencephalogram in one patient and minimal slow wave activity in the temporal region in another were described by Denny-Brown.[10] A large amount of delta activity in the frontal and parietal areas was reported in one case by Gross.[17] The report of Askenasy and Wijsenbeek[4] included a description of the electroencephalographic pattern of three of their four cases. In one a normal record was obtained. The lesion in this case was probably of traumatic origin and had been incurred ten years previously. Two to six per second waves and diminished alpha activity in the occipital, posterior parietal, and temporal areas were observed in another. Their third case disclosed slow waves of low to medium voltage over the entire hemisphere on the affected side, most pronounced in the temporo-occipital region. Slow wave foci in the temporal area were reported by Bonnal and associates.[7] These authors further stated that concomitant with clinical improvement, the electrical pattern became less abnormal. Delta activity in the parietotemporal region early in the course of the disease is a characteristic finding according to Gurdjian and Webster.[18] They further state that as the condition becomes chronic, the electroencephalogram reverts to normal, even in patients with considerable neurologic deficit. Delta foci in the frontotemporal region were also reported in two of three cases by Müller.[29] In five out of our seven cases, there was a slowing of alpha with some diffuse delta activity, usually with focal accentuations at the frontal and temporal electrodes, all on the affected side. In only one case was the electroencephalogram entirely normal. Judging thus from our own experience and the available literature, it would appear that electroencephalographic abnormalities are observed much more frequently in thrombosis of the internal carotid artery than in the other varieties of cerebrovascular occlusive disease.

Occlusion of the internal carotid artery usually takes place in the neck just distal to the bifurcation of the common carotid artery. Less often the intracranial portion of the artery in the region of the siphon is affected. Bilateral occlusion of the internal carotid artery[24,34] as well as involvement of the common, external, and internal arteries has been reported.[16,36]

In those instances in which angiography of the uninvolved side has been performed, usually the dye has also been observed to outline the anterior cerebral circulation of the affected hemisphere. Visualization of the Sylvian vessels on the side of the occlusion has occurred less frequently.

An anastomosis between the internal and external carotid arteries by way of the superficial temporal and internal and external maxillary arteries and eventually the ophthalmic artery has occasionally permitted dye to outline the intracranial circulation in the presence of an occlusion of the cervical portion of the internal carotid artery. Such cases have been reported by Marx,[24]

Denny-Brown,[10] and Shapiro.[31] According to Denny-Brown,[10] such anastomosis is accompanied by a mild degree of proptosis and has been observed no earlier than six weeks after carotid occlusion. It had not resulted in clinical recovery in his experience.

The available data bearing on the genesis and pathology of this disorder have been well summarized by Johnson and Walker[20] and by Cloake.[9] According to Cloake, a "thorough correlation of cerebral and arterial pathology in postmortem examination has been rarely obtained and the full study of the pathology of the disease remains unsatisfactory." Arteriosclerosis and thromboangiitis obliterans appear to be the most significant causative factors, the former probably being much more important. In a study of 3,500 necropsy specimens, Hultquist[19] found macroscopic evidence of thrombosis of the carotid arteries in 69 cases. The etiology in each instance was arteriosclerosis. Others including Sorgo,[32] Andrell,[2] Webster and co-workers,[36] and Fisher[14] have presented additional histologic evidence substantiating the relative importance of arteriosclerosis. Most commonly the arteriosclerotic process affects the vessel at its origin. The region of the carotid sinus was selectively involved in the four cases studied by Fisher. The lumen of the vessel was either nonexistent or considerably narrowed. Microscopic examination disclosed no changes involving the adventitia or media. Subintimal connective tissue containing atheromatous material and endothelial lined spaces occupied the lumen.

Thromboangiitis obliterans involving the internal carotid artery has been described,[21] as well as the concomitant occurrence of cerebral thromboangiitis obliterans and thrombosis of the internal carotid artery resulting from arteriosclerosis.[3,32]

According to Hultquist[19] the changes in the brain are most marked in the cortical and subcortical areas corresponding to the anterior and central distribution of the middle cerebral artery. Involvement of the outer portion of the lenticular nucleus, the anterior limb of the internal capsule, the head of the caudate nucleus, the insula, and large areas of the frontal lobe was reported by Fisher.[14]

The exact mechanisms underlying the clinical manifestations of thrombosis of the internal carotid artery are not fully understood. It is apparent that in the absence of associated disease of the cerebral blood vessels, the clinical picture following occlusion of the internal carotid artery will depend on the adequacy of the collateral circulation. The variable results following ligation attest to this. The explanation of transient attacks and of the progressive course so often observed in this condition is not altogether clear. It is conceivable that increasing cerebral ischemia attendant upon gradual obliteration of the carotid artery in a patient with an insufficient collateral circulation would result in a progressive neurologic deficit. To account for the episodic attacks various hypotheses have been proposed. Cerebral vasospasm, embolization from the thrombus, concomitant disease of the cerebral blood vessels, and a drop in blood pressure inducing or accentuating a state of cerebral

vascular insufficiency have been suggested as possible etiologic factors. Moniz and co-workers,[27] Andrell,[2] and others attributed the evanescent neurologic symptoms to spasms of the cerebral arteries resulting from a reflex action initiated in the diseased carotid artery. Evidence that cerebral emboli may originate in a thrombotic lesion involving the carotid bifurcation was presented by Chiari.[8] According to Denny-Brown,[10] "the transient cerebral disorders, which are cited as examples of 'vasospasm' have in common a defective collateral circulation. The primary event is occlusion of a cerebral vessel, not by spasm but by endarteritis. The repeated transient disorders reflect the sensitivity of the tissue, thus indirectly supplied by collateral vessels, to fluctuations in systemic blood pressure." He[11] further stated that . . . "Any severe fall in blood pressure, such as that associated with syncope or intestinal hemorrhage, is likely to provoke a catastrophic necrosis of a large part of the area supplied by the middle cerebral artery." Elvidge and Werner[13] are of the opinion that "there is no direct causal relationship between a thrombosis of the internal carotid artery and the neurologic picture. Symptoms and signs depend upon which of the cerebral branches is or are involved. This involvement may be secondary to a thrombosis of the internal carotid artery, but oftener, in our opinion, both are independent manifestations of the same disease." Cloake[9] considers it probable that in some cases at least the clinical symptomatology is due to changes in the cerebral arteries themselves, caused by arteriosclerosis or thromboangiitis obliterans and antedating the thrombotic lesion of the internal carotid artery.

No form of treatment, including cervical sympathectomy, excision of the involved segment of artery, and the use of anticoagulants, has proved unequivocally effective. Removal of the thrombosed segment has been advocated for the purpose of interrupting sympathetic vasoconstrictor fibers and as a prophylaxis against embolization. It is extremely doubtful whether surgical removal of the clot, as suggested by Strully and co-workers,[33] will prove feasible or beneficial. If the view that thrombosis of the internal carotid artery most often is part of a generalized vascular disorder is correct, the therapeutic outlook is even less encouraging. Though admittedly hazardous, anticoagulant therapy possibly merits further trial. The prognosis is guarded but improvement may occur. Some degree of neurologic deficit persists as a rule.

SUMMARY

Seven cases of spontaneous occlusion of the internal carotid artery, encountered among approximately 500 cases studied by angiography for suspected brain tumor or vascular anomaly, are reported. The literature is briefly reviewed. Clinical manifestations are discussed and the pathogenesis of the syndrome considered.

On clinical evidence alone, the diagnosis often cannot be made with certainty. The arteriograms in these cases are definitive.

The frequency and character of the electroencephalographic changes are indicated.

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Cerebrospinal Fluid Changes Following Closed Craniocerebral Injuries

*Richard A. Davis, M.D.**

DURING the two year period between July 1951 and July 1953, 546 patients were admitted to the enlisted men's neurosurgical ward at the United States Naval Hospital, National Naval Medical Center, Bethesda, Maryland. Craniocerebral injuries accounted for 222, or 40.6 per cent of all admissions. Open craniocerebral injuries (60 patients) were not as frequent as the closed type which occurred in 162 patients. The majority of these craniocerebral injuries were sustained as a result of automobile mishaps.

Forty-three of the 162 patients with a closed head injury were studied. They had no evidence of a fracture through the calvarium or base of the skull on x-ray examination; there was a period of unconsciousness greater than five minutes; a diagnostic lumbar puncture was performed, with a careful manometric study and biochemical determinations; and a complete neurologic examination was performed for all patients under study. Lumbar punctures were done with the patient in the lateral position, and the cerebrospinal fluid was sent to the laboratory immediately for examination. One of the most difficult problems was an accurate determination of the period of unconsciousness; in most instances estimates were recorded, having been verified by information from relatives, police, witnesses to the accident, and other emergency service personnel who might have seen the patient first. In none of the patients did cerebrospinal fluid and blood escape from the nose, ears, or nasopharynx.

OBSERVATIONS

An occasional investigator[1,2] has been concerned with cerebrospinal fluid findings immediately following a closed head injury, but no figures are available for periods varying up to months or years after trauma. A wide range of severity of injury is represented in the 43 cases reported here; there were periods of unconsciousness varying from five minutes to 21 days. In only six patients were the cerebrospinal fluid studies normal.

The following values for the cerebrospinal fluid were accepted as normal: protein 28 mg. per cent, with a range of 15 to 45 mg. per cent; sugar 65 mg.

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The opinions expressed herein are those of the author and not necessarily those of the Department of the Navy.

per cent, with a range of 50 to 80 mg. per cent; chlorides 726 mg. per cent, with a range of 697 to 748 mg. per cent; and the range of cerebrospinal fluid pressure by lumbar puncture, 70 to 180 mm. of water.[3] Cerebrospinal fluid chemistries were not considered abnormal unless they exceeded the figures designated as the highest limit of normal range. Based on previous work,[1] 100 red blood cells per cu. mm. of cerebrospinal fluid was considered to be a significant elevation, as this figure allowed an ample margin for minor bleeding at the time of lumbar puncture.

In this series of 43 patients the protein content ranged from 6 to 162 mg. per cent, with an average of 43 mg. per cent, and was elevated in 18 patients. In eight patients the cerebrospinal fluid contained significant numbers of erythrocytes. Sugar ranged from 43 to 115 mg. per cent, with an average of 80 mg. per cent, and was increased in 19 patients. Chlorides were abnormally low in two patients and elevated in ten, with an average of 735 mg. per cent. The cerebrospinal fluid pressure was increased in 18 instances and averaged 187 mm. of water for all patients; a globulin fraction was present in three patients; the cerebrospinal fluid was xanthochromic in four instances.

CEREBROSPINAL FLUID CHANGES AND NEUROLOGIC DEFICIT

There were 19 patients who exhibited neurologic signs following the closed type of head injury, and lasting damage was evident in four patients. The neurologic changes varied from transient pupillary differences, decreased deep tendon reflexes, and facial asymmetry, to permanent deficits involving the upper motor neurone level. Of these patients, the cerebrospinal fluid showed an elevated protein level in 11; increased intracranial pressure in nine; significant numbers of erythrocytes in six; abnormally high chlorides in four; and elevated cerebrospinal fluid sugar in four. There were two patients with neurologic findings who had normal cerebrospinal fluid values.

In the presence of a neurologic deficit, it would be reasonable to expect that the extent of neural damage might be reflected in some way in the cerebrospinal fluid. This supposition is supported to some degree by the fact that the protein level and erythrocyte counts were high in approximately 90 per cent of this group of patients. The increased protein probably represented the products of glial degeneration and cleavage of red blood cells, and, as stressed by Russell,[2] its level does not necessarily coincide with the amount of blood present.

CEREBROSPINAL FLUID CHANGES AND THE STATE OF CONSCIOUSNESS

The 43 patients were grouped in three categories depending on the length of the period of unconsciousness: 1) 19 patients (44.1 per cent) were unconscious for more than five minutes but less than one hour, with an average period of 20 minutes; 2) 13 patients (30.2 per cent) were unconscious for more than one hour but less than 24 hours, with an average period of 5.5 hours; 3) 11 patients (25.5 per cent) were unconscious for more than 24

hours, with an average duration of nine days. The shortest period of coma was three days and the longest was 21 days.

In the first group of 19 patients, three had normal cerebrospinal fluid determinations. The manometric readings were elevated in ten patients (average 230 mm. of water); sugar was increased in 11 cases (average 89 mg. per cent); there were three patients with increased numbers of erythrocytes in the fluid; and six patients had elevated protein levels (average 57 mg. per cent). In the majority of patients lumbar puncture was performed within 90 hours following trauma, which may account for the high incidence of increased cerebrospinal fluid pressure and elevated sugar levels. The protein was increased in six patients and, in general, did not bear any relation to the time elapsed between the injury and the lumbar puncture. This is illustrated by one patient who reentered the hospital two years and nine months after having sustained a "minor" head injury (unconscious 15 minutes), still complaining of severe headaches similar to those at the time of discharge. On two separate occasions the cerebrospinal fluid showed protein levels of 45 mg. per cent and 54 mg. per cent.

Two of the 13 patients in the second category (unconscious for more than one hour but less than 24 hours) had normal cerebrospinal fluid findings. The protein level was increased in five patients (average, 71 mg. per cent); abnormal chloride values were present in five cases, with four being elevated and one well below normal as a result of vomiting following injury (average, 740 mg. per cent); sugar was increased in five instances (average, 96 mg. per cent); the cerebrospinal fluid pressure was increased in four cases (average, 190 mm. of water); erythrocytes were present in significant numbers in two patients; and the globulin fraction was present in three patients.

The cerebrospinal fluid pressure in this group presents a contrast to those in the first group; only one reading above 200 mm. of water was obtained. Possibly the patients were in shock when lumbar puncture was performed, or collections of cerebrospinal fluid had formed over the cortex to reduce the pressure substantially. Elevated sugar levels were found at short intervals following the head injury in this group of patients, but such elevations were not encountered when the lumbar puncture was performed at successively longer time intervals. The early sugar elevations, as in the first group, may reflect the acuteness of injury.

In the third group of 11 patients (unconscious for periods longer than 24 hours), the average duration of coma was nine days, with a range between three and 21 days. All of these patients were treated by conservative measures and all recovered, but with variable residual neurologic findings. There was one patient in this group who was unconscious for five days, and had normal cerebrospinal fluid chemistries and manometric determinations.

Protein was most frequently elevated in this group of patients, with high values in seven patients (average, 80 mg. per cent); increased numbers of red blood cells were present in three patients; the cerebrospinal fluid pressure

was increased in four cases (average, 245 mm. of water). There was a significant correlation between the period of unconsciousness and the protein level of the cerebrospinal fluid; individuals who were unconscious for long intervals consistently had high protein determinations. Both the sugar and chloride levels were increased in only three patients, as compared to frequent high levels in the less severely injured patient of the first two categories. Of all the patients with elevated manometric studies only four were unconscious for more than 24 hours, which suggests that the pressure bears little relation to the state of consciousness.

CEREBROSPINAL FLUID FINDINGS AND SYMPTOMS

The most common complaint following closed craniocerebral trauma was headache, followed in frequency by nausea and vomiting, and then dizziness, loss of consciousness, and convulsions. Of the 30 patients who complained of headache at one time or another following the injury, there were 18 who had increased cerebrospinal fluid pressure, the approximate average of which was 225 mm. of water. The greater percentage of complaints of headache was during the patient's period of hospitalization, but six were re-admitted with this complaint and 11 patients had pneumoencephalograms performed because of this symptom. There were five patients who had significant number of erythrocytes in the cerebrospinal fluid, which may be an important factor in posttraumatic headache. Multiple episodes of nausea and vomiting occur frequently following closed head injuries[2] and were present in ten patients. The cerebrospinal fluid chloride level reflects that of the blood and so would be depressed following an extensive period of vomiting; this was verified in two patients. Three patients had brief episodes of unconsciousness following the initial period of coma, and one of these was reported to have had a convulsion although this was not verified. Other less frequent complaints included dizziness, weakness in the extremities, chest and abdominal pain, visual changes, and tinnitus.

CEREBROSPINAL FLUID FINDINGS AND SEQUELAE

There were 12 patients (27.9 per cent) who were considered to have permanent, disabling sequelae as a result of the craniocerebral injury; eight individuals were separated from service with a posttraumatic neuropsychiatric diagnosis (organic psychosis, anxiety reaction, latent schizophrenic reaction, and emotional immaturity reaction); four patients were discharged from the service because of a permanent neurologic deficit following the closed head injury. Of the eight patients discharged with a neuropsychiatric diagnosis, four had elevated cerebrospinal fluid protein levels (average, 64 mg. per cent); there were no cases with increased numbers of erythrocytes in the fluid and none with elevated manometric studies. Of the four patients who had permanent neurologic defects, there were three who had high cerebrospinal fluid protein levels (average, 65 mg. per cent); two patients had significant numbers

of red blood cells. The correlation between neurologic and psychiatric sequelae and the protein level appears to be close.

Moderately severe sequelae included symptoms such as disorientation, confusion, and intervals of memory loss for various periods of time. There were 16 patients who demonstrated some posttraumatic disturbance of higher cerebral function. Nine patients were considered to be severely disoriented and confused for periods of more than seven days after regaining consciousness, and psychotic behavior was not uncommon in this group. There were seven patients who regained consciousness and then were moderately confused for less than 24 hours after the head injury; some patients in this group complained of memory disturbance at various times following trauma. The cerebrospinal fluid changes in this group of 16 patients included the following: eight had elevated protein levels (average, 61 mg. per cent); five showed increased manometric readings (average, 230 mm. of water); and the sugar level was high in seven, with an average of 88 mg. per cent.

DISCUSSION

The literature contains little material devoted specifically to the changes which are observed in cerebrospinal fluid determinations of the patient who has sustained a closed craniocerebral injury. The time at which the lumbar puncture was performed following head injury was a variable factor, ranging in this series of 43 cases from three hours to two years and nine months. This suggests that cerebrospinal fluid abnormalities and clinical symptoms and signs may coexist at both brief and rather lengthy intervals following closed head injury. It is generally assumed that the patient who is unconscious for periods of minutes up to 12 to 24 hours will probably have a normal cerebrospinal fluid, and the fact that consciousness has been regained usually obviates the necessity to perform a lumbar puncture. Cerebrospinal fluid studies were normal in only six of these 43 patients.

One of the most frequent abnormal cerebrospinal fluid findings following closed craniocerebral injury was an elevation in the pressure of the fluid. Others[2] have emphasized that there is practically no correlation between the state of consciousness and manometric pressure, and this point has been further substantiated by this group of patients. Intracranial pressure was most frequently elevated in the patient unconscious from five minutes to one hour. In the more severely traumatized patient who was unconscious for greater intervals, the intracranial pressure was usually decreased. A logical explanation is that the decreased pressure reflected a state of shock or, later, neuropathologic changes over the cerebral cortex which caused a pooling or collection of fluid. Of all the clinical factors under consideration, the symptom of headache and the finding of increased intracranial pressure were most closely correlated. However, in patients with neuropsychiatric sequelae, who frequently mentioned pain in reference to the head, all manometric studies were normal. Similarly, there was little or no correlation between increased intracranial pressure and the neurologic deficit.

An elevation in cerebrospinal fluid protein appeared to be the most accurate guide to severity of the injury, and there was good correlation with the period of unconsciousness. Study of the three categories of patients, based on increasing periods of unconsciousness, showed that the frequency of elevation in the protein level increased proportionately as did the length of coma; this protein elevation was generally independent of significant amounts of red blood cells. The protein level usually reached a higher level when estimated at early intervals following the injury, but abnormally high determinations were not infrequent many weeks or months after the injury. In the patients who were separated from the service with a neuropsychiatric diagnosis and the group with a permanent neurologic deficit, the most frequent abnormal cerebrospinal fluid determination was increased protein. As an indicator to the severity of injury, the protein may represent the breakdown and cleavage products of glial tissue as well as erythrocytes and serum.

Hyperglycemia and frank glycosuria following craniocerebral injury are of frequent occurrence,[2] so that elevated sugar levels in the cerebrospinal fluid occurring in 19 (44.1 per cent) of the patients was not unexpected. The time at which the lumbar puncture was performed following injury was of more importance in this determination, and in most instances this was 90 hours. Increased sugar levels were present in the patient unconscious for more than five minutes but less than one hour. While the frequency of increased protein levels varied in direct proportion to the length of unconsciousness, the frequency of high sugar determinations had an inverse ratio to the length of coma. It would be assumed that the elevated sugar level reflected the acuteness of the craniocerebral injury. It is a known fact that sugar is decreased in the presence of large numbers of erythrocytes in the cerebrospinal fluid,[3] but in most instances the number of red cells present was not large enough to exert influence.

Presence of a significant number of red blood cells in the cerebrospinal fluid was not a reliable guide to severity of the closed craniocerebral injury without fracture of the calvarium and disruption of the dura mater. Although one-third of the patients with a neurologic deficit had significant numbers of red blood cells in the fluid, there were only three with this finding who were deeply comatose for more than 24 hours. Of the 18 patients with abnormally high protein levels, only five had more than 100 red blood cells per cu. mm. of cerebrospinal fluid, suggesting that the protein could have originated from a source other than the breakdown of erythrocytes.

The cerebrospinal fluid chloride content depends on the concentration of chloride in the serum, which in turn is decreased after vomiting and in the presence of fever and is increased when renal function is impaired. In this series, there were two patients with protracted vomiting following head trauma, and both had decreased chloride values in the cerebrospinal fluid. There were ten patients who had elevated chlorides, which might well represent impaired renal function on the basis of prolonged hypotension following cranio-

cerebral injury. There was little or no correlation between any of the clinical findings and chloride determinations.

CONCLUSIONS

1. In a study of 43 patients with a closed head injury, the protein level was the most accurate cerebrospinal fluid guide to the severity of craniocerebral injury. The frequency of protein elevation generally varied directly with the length of unconsciousness. The level was increased in patients with permanent neurologic deficits and those who had neuropsychiatric disturbances.

2. When the determination was made within 90 hours following injury, the cerebrospinal fluid sugar value varied inversely to the period of unconsciousness and indicated the acuteness of the craniocerebral injury.

3. The presence of more than 100 erythrocytes per cu. mm. in the cerebrospinal fluid was not a reliable guide to the severity of the craniocerebral injury with absence of fracture through the calvarium. Protein elevations were usually independent of the elevated number of red cells in the cerebrospinal fluid.

4. There was no correlation between the state of consciousness and the intracranial pressure. However, most of the patients who had headaches following injury had an increased manometric reading.

5. The chloride level of the cerebrospinal fluid was of little diagnostic importance in closed craniocerebral trauma, but did show a change following severe vomiting.

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Occasionally, after a fit, or, more frequently, after a series of fits, an attack of mental disturbance may come on which lasts for several days. It may be simply a demented state, or there may be hallucinations, with irritability and even violence. In the latter cases, according to Voisin, there may be an elevation of temperature to 102° or 104°. This state sometimes comes on in an epileptic patient without immediate association with attacks, and even during the temporary cessation of attacks. It is not uncommon for a patient's mental state to be worse, his temper more irritable, during the temporary cessation of severe fits, and this apart from the occurrence of slighter seizures, and in rare cases the disturbance amounts to actual mental aberration.

W. R. Gowers in *Epilepsy and Other Chronic Convulsive Diseases,* published in 1885.

Homonymous Hemianopia in Multiple Sclerosis

Max Chamlin, M.D. and Leo M. Davidoff, M.D.

In 1950 Savitsky and Rangell[1] made an exhaustive study of the incidence of homonymous hemianopia in multiple sclerosis, and showed that it was so rare they were not able to find a single instance among 682 cases. Of this number, 50 were cases verified at postmortem examination at the Montefiore Hospital, 217 were gathered from the literature, and 415 were observed clinically. In the same paper, they quoted from an extensive bibliography bearing out essentially the same point. Alpers[2] claimed that homonymous hemianopia, though rare, has been noted in multiple sclerosis, while Oppenheim,[3] Rea,[4] and the National Multiple Sclerosis Society[5] have reported its occasional occurrence in multiple sclerosis. A number of cases have been cited in which there were no necropsy reports to verify the diagnosis of multiple sclerosis. This is a justifiable criticism, especially in view of the fact that 24 of the 217 verified cases from the literature had associated organic disease of the nerves and/or brain other than multiple sclerosis, and four of the 50 verified cases had such concomitant organic disease.

Savitsky and Rangell[1] also quoted from the work of Uthoff,[6] who, in his classic paper on the ocular symptoms of multiple sclerosis, noted the absence of homonymous hemianopia in his series of 100 cases. Gipner[7] made a similar observation in another series of 100 cases studied ophthalmologically. Velter[8] studied 63 cases carefully, four of which were autopsied; in none of them was there any evidence of homonymous hemianopia. Windmuller[9] found no homonymous peripheral field defect in 90 cases studied ophthalmologically.

Despite the absence of the homonymous hemianopic defects, Uthoff[6] noted in 1890 that there was evidence of multiple sclerosis lesions in the visual pathways, and Muller made a similar observation in 1904 on the rarity of the occurrence of hemianopic defects in multiple sclerosis, despite the frequency of the lesions in the chiasm. Savitsky and Rangell[1] likewise stated that they had repeatedly observed lesions of multiple sclerosis in the optic pathways, without any evidence of any hemianopic field defect during life. Lenz,[10] writing in 1909 on the causes of hemianopia in 967 verified cases, did not even mention multiple sclerosis. Savitsky and Rangell[1] quoted seven additional series with a total number of 1,199 cases of multiple sclerosis, with not a single

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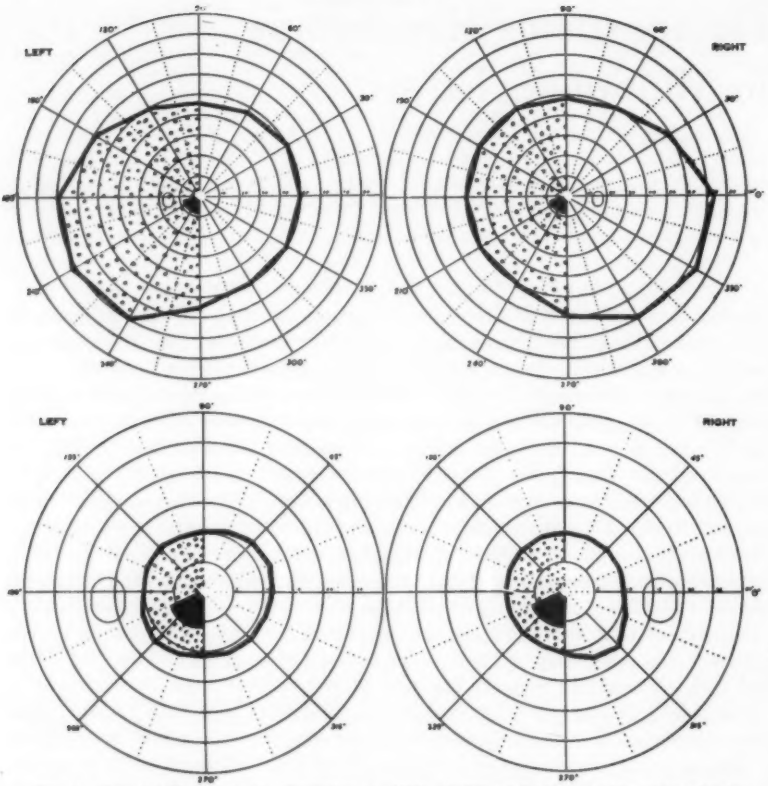

FIG. 1. *(Case 1.) Chart 1* (top). December 11, 1952. Peripheral fields for 2/330 white, showing left homonymous hemianopic defect with macular sparing and dense paracentral component for 20/330 white. All defective areas are absolute for stated test objects.
Chart 2 (bottom). December 11, 1952. Central field study for 1/2000 white. Left homonymous hemianopia with dense paracentral component for 40/2000 white.

instance of homonymous hemianopia. In 1951 Yaskin, Spaeth, and Vernlund[11] reported on the ocular manifestations of 100 consecutive cases of multiple sclerosis, with no mention of a homonymous hemianopic defect. More recently, Wybar[12] reviewed the ocular findings in 91 consecutive cases of multiple sclerosis, and no cases of homonymous hemianopic defect were found.

The only reports in the literature showing homonymous hemianopic visual field defects in multiple sclerosis are those of Traquair[13] and Malbran and co-workers.[14] Traquair reported two cases with paracentral homonymous hemianopic defects which he believed were due to multiple sclerosis. While he did not have necropsy material to prove these cases, he felt that the clinical data were adequate for the diagnosis. Malbran and his co-workers cited a single case of homonymous hemianopic paracentral scotoma in a 33 year old

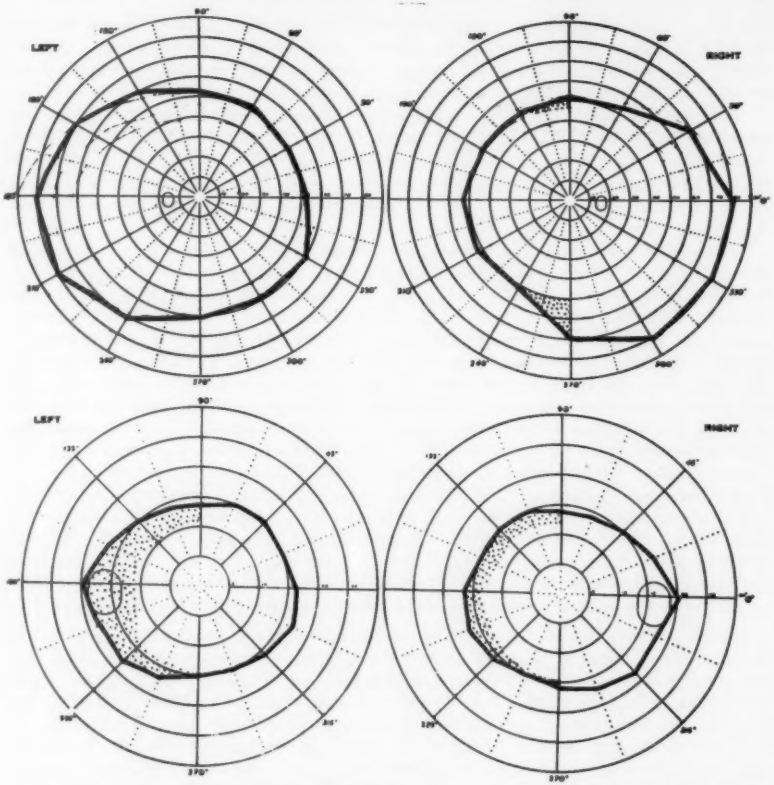

FIG. 1. *Chart 3* (top). January 23, 1953. Patient reports complete clearing of her visual field defect. Peripheral field for 2/250 white shows only a slight qualitative difference[15] nasally, in the right eye, above and below. No paracentral homonymous defects.

Chart 4 (bottom). January 23, 1953. Central fields for 1/2000 white show only a slight left homonymous defect, but no more paracentral components.

woman whose entire clinical picture was that of a demyelinizing process such as multiple sclerosis. Thus, these three cases stand out rather conspicuously among the many hundreds of cases of multiple sclerosis in which homonymous hemianopic defects were not found.

It is apparent, therefore, that homonymous hemianopia in multiple sclerosis is certainly a rarity. Of the several hundreds of cases of bitemporal hemianopia as well as homonymous hemianopia examined in the past few years, there was not a single instance in which the diagnosis of multiple sclerosis was considered justified until the four cases reported here were encountered.

Case 1.—A 36 year old white widow was examined on December 11, 1952. She had a history of a sudden loss of vision in her left eye in July 1952. At that time she was exam-

ined by an ophthalmologist, who made a diagnosis of retrobulbar neuritis. During the next three weeks visual function returned completely, according to the patient's story. On December 1 she suddenly experienced blurring of vision in both eyes and was examined by the same ophthalmologist, who now found a left homonymous hemianopia.

Physical examination showed increased reflexes bilaterally and ankle clonus which was not sustained. There was poor bilateral plantar flexion. Ocular examination showed both disks to have slightly fuzzed margins, but no cups and no venous pulsations. The left disk did not look particularly pale. However, the visual field examination revealed a definite left homonymous hemianopia, with a dense homonymous paracentral component and macular sparing (figure 1).

The patient was admitted to the hospital; laboratory tests including urinalysis, a complete blood count, roentgenograms of the skull, and an electroencephalogram were normal. She returned six weeks later, at which time she complained of paresthesias in both legs, weakness of the left lower extremity, and difficulty in walking. Examination at this time revealed that the right pupil was slightly larger than the left. She had a spastic, staggering gait, with some weakness of the left lower extremity and a positive Babinski sign bilaterally. The abdominal reflexes were absent. There was a sustained ankle clonus in both lower extremities. Visual field examination was performed again and this time the peripheral fields showed no evidence whatever of any homonymous hemianopic defect for 1/250 white and 2/250 white. With 1/2000 white, there was only a very faint suggestion of some minimal residual upper homonymous hemianopic defect, but this was rather dubious. There was no question but that the dense homonymous hemianopic defect had cleared almost completely. At this time a pneumoencephalogram was done, which revealed normal and symmetrical filling of all the ventricles. The third and fourth ventricles were well outlined and normal in size, shape, and position. There was a little more subarachnoid gas, bilaterally, than usual, but no evidence of any mass lesions.

A clinical diagnosis of multiple sclerosis was made, and the patient was discharged.

Case 2.—A 26 year old white male student was first seen in January 1951 with a history of a gradual onset of weakness, first in the right leg and then in the left, about one year previous to examination. In September 1950 he recovered entirely. In November 1950 he experienced a fainting attack following several days of dizziness. Shortly after this he noticed numbness and tingling in the legs up to the waist. He was admitted to the neurologic service of a large medical center at that time, and myelography was performed and reported to be normal. Spinal fluid examination showed four white blood cells with a negative Pandy colloidal and a gold curve of 11111000000; serology studies for syphilis were negative and the total protein was 41.3 mg. per cent. There was a history of poor vision since an eye operation 16 years before.

On examination in January 1951 the following findings were made: The left pupil was larger than the right. There was a slight horizontal nystagmus. The other cranial nerves appeared intact. Motor power was good in both arms. There was no ataxia of the upper extremities and no Hoffmann sign. The tendon reflexes in the arms were normal. The right upper and lower abdominal reflexes were diminished. The patellar reflexes were normal. No Babinski signs were present. The right Achilles reflex was diminished. There was a slight diminution of sensation in the right foot. The presumptive diagnosis was multiple sclerosis. The patient was reexamined in March 1951, at which time there seemed to be some improvement in his symptoms, although he swung his right leg a little more than normal in walking. In May 1951 he again complained of dizzy spells with double vision. At this time only the left upper abdominal reflex was obtained.

On September 6, 1952, ophthalmologic examination was carried out. Visual acuity with best correction was 20/20 in the right eye and 20/60 in the left eye. He stated that for about a year he had had some disturbance of central vision in his right eye, which was the so-called "good" eye. During the previous summer he had realized that he could not see very well to the left of the midline. External examination was not remarkable and

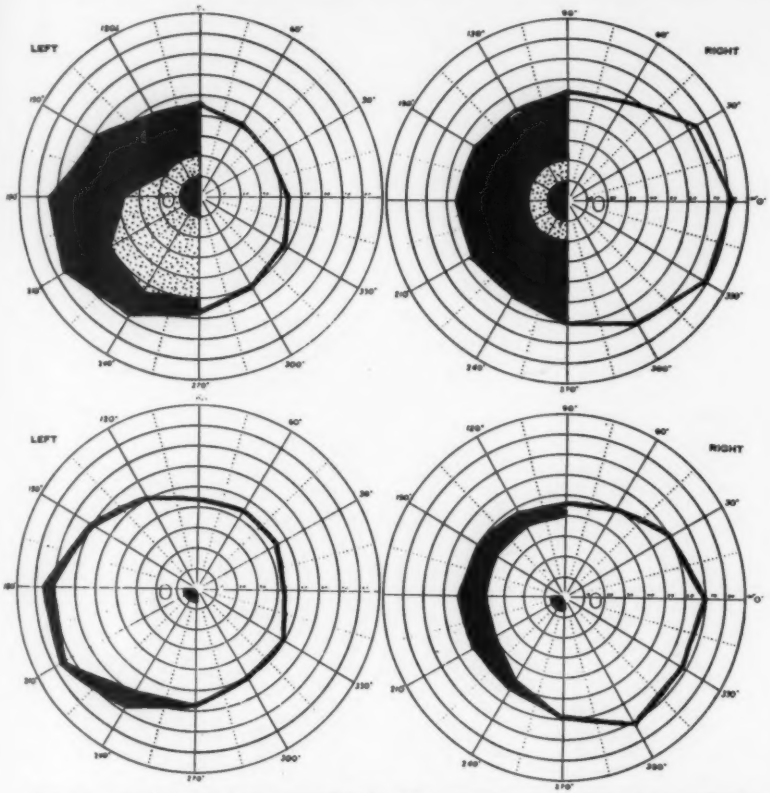

FIG. 2. *(Case 2.) Chart 1* (top). September 6, 1952. Peripheral field shows a left homonymous hemianopia. The outer blackened area represents defect for 10/330 white above and for 3/330 white below. The dotted area represents defect for 2/330 white. The paracentral components are dense even for hand movement.

Chart 2 (bottom). January 31, 1953. Peripheral field for 2/330 white showing almost complete filling out of the periphery, with only very slight defect left there. However, a very small paracentral homonymous hemianopic defect remained even for 10/330 white.

extra-ocular motility was not restricted, but there was a tendency for some exophoria-tropia and convergence was not possible. The media were clear and both disks showed good margins and deep cups, as well as good color. Complete visual field studies were made. There was a left homonymous hemianopic defect for 2/330 white, as seen in figure 2. Roentgenograms of the skull were normal. An electroencephalogram showed no abnormalities. A repeat examination on September 24 showed no remarkable change in the visual fields, but numbness in the left leg present for ten days was described.

On January 15 the patient reported several episodes of extreme weakness and unsteadiness on his feet. While walking the right leg had to be thrown outward, with some degree of ataxia. The visual fields were reexamined on January 31, 1953, and at this time there was almost complete filling out of the left peripheral homonymous field that had previously been defective. A small, dense, paracentral homonymous scotoma was retained.

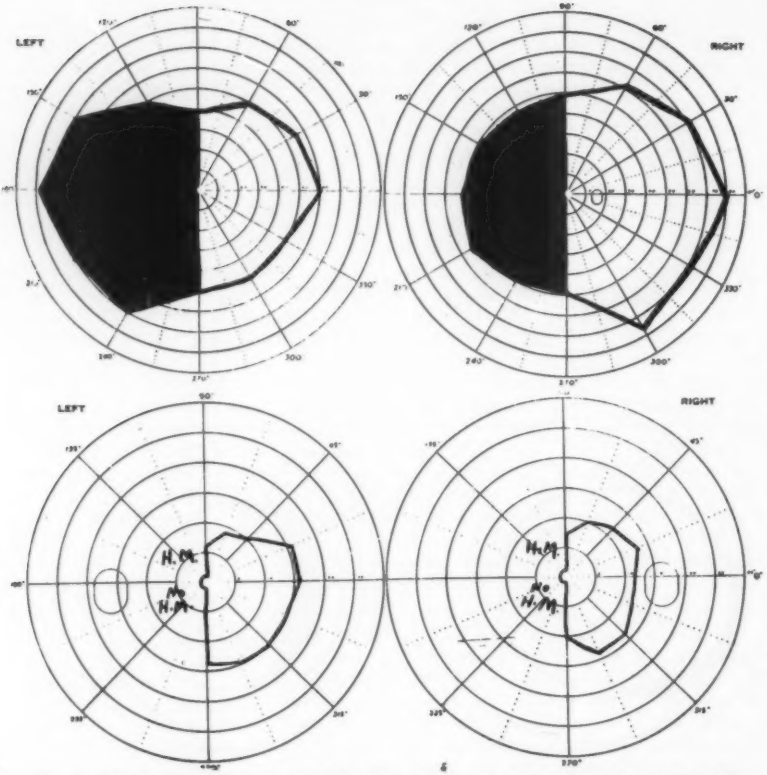

FIG. 3. *(Case 3.) Chart 1* (top). April 10, 1953. Peripheral field for 2/330 white shows left homonymous hemianopia with macular sparing.
Chart 2 (bottom). April 10, 1953. Central field for 1/2000 white, the left homonymous field being defective and quite dense, there being no hand movements below the horizontal, and hand movements barely visible above the horizontal.

In view of the recurrences and remissions of disseminated signs and symptoms and of the laboratory findings, a diagnosis of multiple sclerosis seemed reasonably certain.

Case 3.—(Examined through the courtesy of the late Dr. Nathan Savitsky). A 22 year old girl was admitted to the Montefiore Hospital on April 7, 1953, with a history of sudden onset of numbness and incoordination of both hands in April 1948. This episode cleared in three weeks. In June 1952 she had experienced sudden weakness of the left leg. Four weeks prior to hospital admission there was onset of blurring in the left half of the field of vision in both eyes, together with numbness and incoordination of both hands. A similar episode of incoordination occurred three months before admission and lasted for a week.

Examination showed the pupils to be equal and normal in size. There was weakness of the left lower extremity with slight diminution of vibratory sensation in the left foot. The abdominal reflexes were absent. There was a bilateral positive Babinski sign. Examination of the visual fields on April 11 revealed a dense left homonymous hemianopia, which was easily demonstrated by gross hand movements. An electroencephalogram revealed a

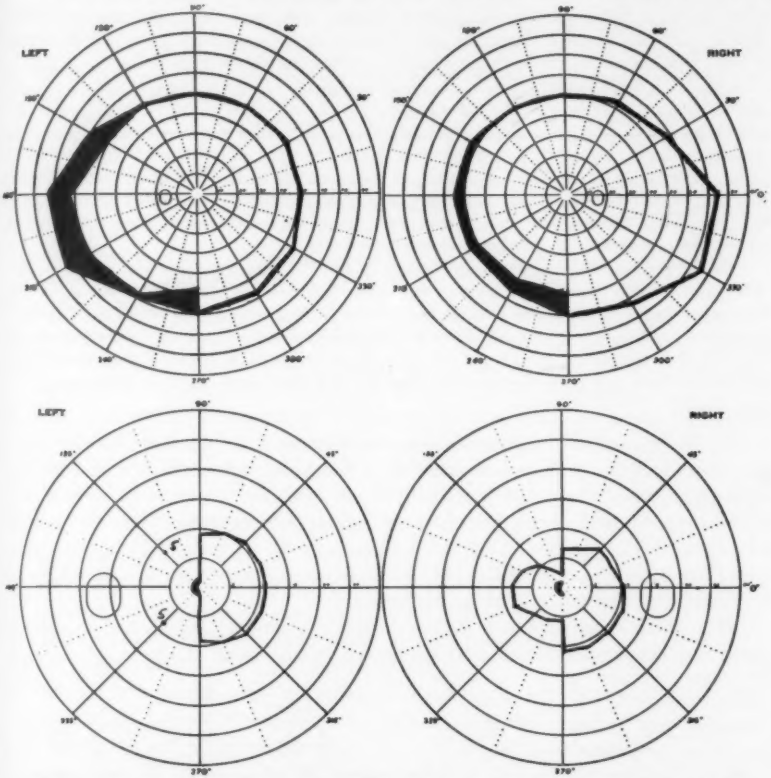

FIG. 3. *Chart 3* (top). June 10, 1953. Peripheral field for 2/330 white shows tremendous clearing, with only a very slight homonymous defect remaining in extreme periphery, especially below. *Chart 4* (bottom). June 10, 1953. Central field for 1/2000 white, showing a great deal of recovery in the central field, with persistence of a very small paracentral defect in the right eye. In the left eye, the small left paracentral defect was much greater, due to the presence of an old caecocentral scotoma from a previous attack of retrobulbar neuritis. Therefore, these two paracentral defects were no longer homonymous. The heavy dot indicates the point at which 5/2000 white is seen, the 5 mm. test object being the smallest one seen there. This method of describing defective field has been described by the authors in a previous article.[16]

moderate degree of diffuse deviation from normal. Roentgenograms of the skull were negative, as were blood tests for syphilis. The urinalysis and blood count were normal. On April 17 a pneumoencephalogram was made, and this showed diffuse atrophy with enlargement of the ventricles and of the cerebral sulci. The spinal fluid was clear and colorless, and contained 28 mononuclear cells. The colloidal gold test with the modified scale developed in the New York State Department of Health was 6, 7, 10, 12, 14, 12, 11, 10, 9, 7, and was interpreted as a so-called D curve, indicative of parenchymatous involvement and highly suggestive of multiple sclerosis. Protein was 78 mg. per 100 cc., and the reaction for syphilis was negative.

The visual field studies are shown in figure 3. It is obvious that on April 10, 1953, there was a dense left homonymous hemianopic field defect, with a dense paracentral sco-

toma. In May 1953 there was considerable clearing. On June 10, 1953, one was barely able to elicit any sort of defect in the peripheral field, while centrally, with 1/2000 white, a very small but dense left lower paracentral homonymous defect remained.

Case 4.—A 35 year old white woman was examined on July 8, 1953. She gave a history of sudden onset of paralysis of the right side of the body in 1950. This lasted for two weeks and then she recovered completely. Six months later she developed unsteadiness of gait, falling to one side when she tried to walk. For the next two years she was completely free of symptoms. In July she again began to fall to her left when walking. She was hospitalized and examined thoroughly at a large medical center, where arteriography and pneumoencephalography were performed. There was no evidence of any intracranial tumor, and a diagnosis of multiple sclerosis was made.

Ocular examination revealed visual acuity of 1/200 in the right eye and 20/30 in the left eye. Complete visual field studies were done, and these showed a complete right homonymous hemianopia. It was difficult to tell from the patient's history whether the severe central loss in the right eye was due to an old amblyopia ex anopsia or a previous attack of retrobulbar neuritis. The disk did not look particularly pale, and thus a diagnosis of old amblyopia ex anopsia seemed reasonable since she did have some degree of hyperopia.

COMMENT

While not verified by postmortem examination, it is believed that the clinical data available in these four cases are reliable enough to make a reasonable clinical diagnosis of multiple sclerosis in each instance. Three of the four cases showed spontaneous clearing of the field defects subsequently, while the fourth was seen only once. Two additional cases seen by us presented similar pictures, but except for the visual field findings clinical evidence was insufficient to warrant a diagnosis of multiple sclerosis.

This rarity of involvement of the posterior pathways stands out in rather sharp contrast to the marked frequency of involvement of the optic nerves,

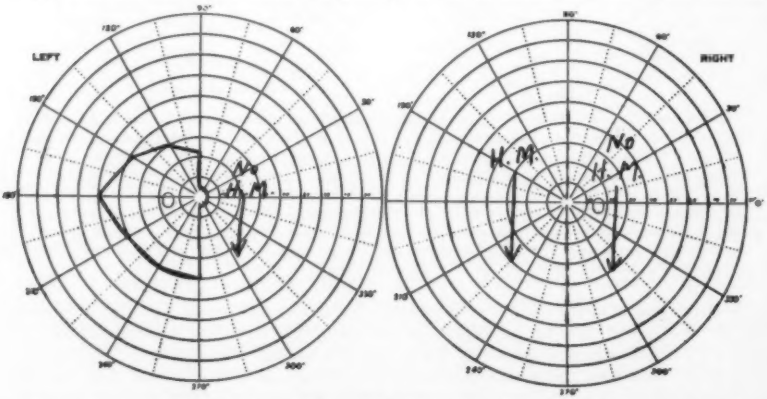

FIG. 4 *(Case 4.) Left eye:* Peripheral field for 3/330 white, showing a nasal defect, even for hand movements, and macular sparing. *Right eye:* Had very poor vision, in the neighborhood of 1/200, probably due to an old amblyopia ex anopsia. Despite this, peripheral field could be estimated with hand movements, which were present nasally and not temporally. Therefore, this picture constitutes a right homonymous hemianopia for hand movements. This patient was not seen again after the initial examination, and therefore it is not known whether or not any clearing took place. The presence of amblyopia exanopsia in the right eye made it difficult to evaluate her central field as regards the amount of macular sparing, if any, and therefore, congruity, if any.

with the resultant optic neuritis or retrobulbar neuritis so frequently seen in multiple sclerosis. It seems possible that involvement of the more posterior portions of the visual pathways by multiple sclerosis may occur later in the disease than does involvement of the optic nerves near the globe. At such later stages other manifestations of the disease may be severe and numerous enough to cloud a mere homonymous hemianopic field defect, and perhaps such field defects therefore go unnoticed. Whether or not the explanation offered is correct, homonymous hemianopia is rarely reported in cases of multiple sclerosis.

It is interesting to note that in case 1 there was evidence of a dense left homonymous paracentral defect at the onset, and in case 2 a residual dense paracentral homonymous defect. In case 3 a dense paracentral defect was seen at the onset, as well as a residual field defect. In case 4, the visual field defect was a completely dense homonymous one at the time of examination, and no particularly dense paracentral components could be discerned.

The paracentral components are particularly interesting, inasmuch as the two cases of Traquair[13] as well as the one case of Malbran[14] also showed dense paracentral homonymous components. This apparent frequency of paracentral defect strongly suggests that the level of the visual pathway involved is rather close to the occipital cortex.

CONCLUSIONS

Homonymous hemianopia is a rare occurrence in multple sclerosis, and its presence should therefore suggest a diagnosis of tumor or vascular disease of the brain. On the other hand, homonymous hemianopia may occur in multiple sclerosis, and four such cases are illustrated. Three of the four cases, as well as three found in the literature, showed dense paracentral components, suggesting that when the lesion of multiple sclerosis involves the posterior pathways, the site of involvement is apt to be near the occipital cortex.

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Epidemiologic Investigations of Amyotrophic Lateral Sclerosis

1. Preliminary Report on Geographic Distribution, with Special Reference to the Mariana Islands, Including Clinical and Pathologic Observations

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COMMENT

Our observations of the clinical and pathologic characteristics of the neurologic disorder we observed in the Mariana Islands lead us to agree with Arnold and associates[1] and with Koerner[2] that this *is* amyotrophic lateral sclerosis and that it is exceedingly prevalent among the Chamorro people, particularly on Guam and Rota. Furthermore, the predominance of males in the patient group, the age distribution, and the course of the disease support the belief that this is a classic form of the disease. There is, as yet, insufficient evidence to identify either some exogenous factor in the environment of the Mariana Islands or heredity as the cause of this unusual situation.

Although the studies now going on may determine whether the cause is predominantly genetic or exogenous, it seems worth while to review the data we now have on hand and to speculate on the possible explanations of the high incidence.

The occurrence of the disease in its highest incidence among the "purest" of the Chamorros of Rota and of Umatac suggests that some characteristic which these people have in common is responsible for the high rate among them. The unique language of these two groups suggests a common ancestry. Umatac is farther away from Rota than any other village on Guam and some of the early people of Umatac, who were renowned for their seagoing ventures, may have settled on Rota after the Spanish Conquest. These people may have carried with them the hereditary taint or some unique cultural custom which is responsible for the disease on Rota. In recent generations, as transportation improved and population mobility increased, the disease may also have spread from Umatac to the rest of Guam and to a lesser extent to Saipan as well.

The first part of this paper was published in the May 1954 issue of NEUROLOGY (4:355-378, 1954).

Koerner found a positive family history in about 40 per cent of his cases. We noted a similar finding in about 35 per cent of our cases. However, familial predisposition may signify either a genetic factor or an environmental factor common to the family, and only accurate pedigrees, which have not been easy to obtain on Guam, will distinguish the relative importance of these factors. Furthermore, in neither Koerner's study nor our own were all family cases located in an unbiased fashion. Often one affected family member would report another patient in his family who had not been known to any of our community-wide case-finding sources. Since a person is generally better acquainted with the illnesses of his own family than of the total community population, such reporting from individual sources may introduce a bias into statistics of familial incidence. The house-to-house survey of selected villages on Guam which is now under way should provide relatively unbiased data on this subject.

On Guam and on Rota, the illness is so prevalent and the average family so large that the occurrence of more than one case in more than a third of the families might not be unexpected, statistically speaking. We had intended to study the relative frequency of consanguinity of parents of patients in the hope that this would aid in determining the role of heredity; but, unfortunately, the Catholic Church records in which dispensations for cousin marriages are recorded for the population were destroyed during the war.

There is some indication in the pedigrees which Koerner[2] presented that the disease sometimes affected parent and offspring. This suggests that the disease might be transmitted as a mendelian dominant characteristic. We are acquainted with only a few other published reports of an apparent genetic form of the disease. In one of these reports, from Barcelona, Spain, a father and son in one family and a father and two daughters in another family developed a classic form of the disease during adulthood.[16] Among the pedigrees we have recently collected at the Mayo Clinic is one of an Iowa family of European descent in which amyotrophic lateral sclerosis appears to have been transmitted as a mendelian dominant trait through four generations.[17] In this family, with 11 out of 23 potentially affected persons having the illness, the sex ratio is about 1:1 for both affected and nonaffected. The group is sufficiently small, however, so that this sex ratio of the affected may be a chance occurrence, even if the cause, presumably genetic, affected a higher proportion of males.

Thus, it is conceivable that the unusual situation on Guam and Rota is due to the presence of an hereditary form of amyotrophic lateral sclerosis. If this is so, we are confronted with two problems: (a) What is the nature of the genetic mechanism which causes the disease? and (b) How can we account for the high frequency of the gene(s) determining susceptibility to the disease on Guam and Rota as compared to other areas?

The published pedigrees as well as our own unpublished data (see above) suggest that the gene concerned is probably an autosomal dominant. The population data available from Guam and from the vital statistics records

of several countries of the Western World (Appendix 1) indicate that the disease occurs about twice as frequently in males as it does in females. Therefore, if all amyotrophic lateral sclerosis is due to the same gene, simple autosomal dominance is ruled out. Dominance with reduced penetrance could explain these data if it is assumed that penetrance is greater in men than in women. ("Penetrance" as used here refers to the percentage of individuals who, when they possess the gene, show any effect from it).

Other possible but less likely explanations of the observed sex ratio among the affected individuals are (1) amyotrophic lateral sclerosis is caused by two different genes, one an autosomal dominant, the other a sex-linked recessive. The former would lead to equal numbers of affected males and females; the latter because of the rarity of the gene would lead to a preponderance of affected males. The combination of these two genes in the proper proportions can give almost any ratio involving an excess of affected males. (2) A second possible explanation would assume that some amyotrophic lateral sclerosis is determined by an autosomal dominant gene and the remainder by some environmental factor which affects males more frequently than it does females. Various other combinations of these are also possible. The pedigrees now being collected may supply the material necessary to decide among these alternatives.

A possible explanation of the high frequency of the gene in the Mariana Islands might be that the trait had been present prior to or was introduced shortly after the time of the Spanish Conquest in the late seventeenth century when the population was so greatly reduced by the war and by severe epidemics of smallpox (which recurred as late as the mid-nineteenth century). However, the reduction of the population following the Spanish Conquest occurred, almost to the point of annihilation, among the people of the northern and central parts of the island: peace came early to the southern villages, including Umatac, and the population in this region was less molested by the warfare, although it was probably affected by the epidemics. Thus, if the trait was introduced among the survivors or if the persons destined to develop amyotrophic lateral sclerosis managed by chance selectivity to survive the war and the smallpox, then it is conceivable that the relative frequency of the gene in Umatac and the entire island would have been greatly increased.*

The persistence of the gene would depend on the reproductive rate of the affected not being significantly impaired; Koerner reported that the average

*It is uncertain how long amyotrophic lateral sclerosis has been prevalent on Guam, or whether the incidence has increased or decreased. Death certificates provide evidence that the disease has been prevalent for at least 50 years. We recently learned of a native legend which states that an Augustinian friar in the village of Umatac declared the curse of "lytico" on adult members of two families in Umatac who had pilfered the friar's mango tree. (Amyotrophic lateral sclerosis, even today, is one of the principal causes of death among the descendants of these same families). As the Augustinian friars arrived on Guam in 1769 and remained there until 1899, the high prevalence may have been first noted sometime during this period.

number of children per patient in his series was nine; we have not yet compared the reproductive rate of the patients to that of the total population. If, however, the reproductive rate of the patient group is less than that of the total population (and this is possible since many patients become ill before they reach the age of 40 years), and if the incidence is not decreasing, the maintenance or the increase of the gene in the population could be explained by assuming a mutation rate sufficiently high on Guam and Rota to produce enough newly mutated genes to at least compensate for those lost because of the reduced fertility of the affected individuals. This assumption presupposes some unusual external or coexistent genetic factor which is responsible for a high rate of mutation among the Chamorros.

Alternately, the gene could be maintained in the population if penetrance is incomplete and if those carrying the gene and who either do not develop amyotrophic lateral sclerosis or develop it late in life are on the average more fertile than the remainder of the population. Finally, some combination of these factors could be operative. Here again the data now being collected may supply the answer.

As of the present writing, the explanation that amyotrophic lateral sclerosis on Guam and Rota is due to the presence of a mutated gene, with a higher penetrance in males, appears most acceptable; but only the forthcoming investigations, which must first seek to identify any causative exogenous factor, will clarify that puzzle.

If the disease were present before the Spanish Conquest of the Mariana Islands and if it is genetically determined or is due to some unique custom in the culture of the Chamorros, then the disease might presumably be prevalent in that part of the world from which the Chamorros originated. However, no unusual prevalence of amyotrophic lateral sclerosis has been reported anywhere in South America or Asia outside of the Mariana Islands, but it is unlikely that this has been studied systematically. The genesis of the early Chamorros is uncertain; some believe they migrated from Argentina, others say from Malaya, Indonesia, Mindanao, or elsewhere in Southeast Asia. If another focus of the disease were discovered in one of these places, it would be presumptive evidence of the origin of some of the Chamorros.

SUMMARY AND CONCLUSIONS

As a result of the observations by Arnold and associates[1] and by Koerner,[2] that amyotrophic lateral sclerosis was highly prevalent on Guam, an epidemiologic investigation in the Mariana and Caroline Islands was carried out.

Forty-two patients were observed on Guam, four patients were found on Rota, and one patient was seen on Saipan. No cases were found in the Truk Archipelago of the Caroline Islands.

On Guam, 120 case reports were collected beginning with the period after Arnold's original observation in 1947. In all but one of these cases the patient was a Chamorro native; the exception was an atypical case of a Japanese who had resided on Guam for many years. No cases have been reported

among the large number of Filipino laborers who are employed on Guam; there is no conclusive evidence to indicate that military personnel stationed on Guam have any greater risk of developing the disorder than those stationed elsewhere.

Although there is some evidence which suggests that the high prevalence of the disease may be due to a genetic trait, the existence of some exogenous etiologic factor, unique to the Mariana Islands, has not yet been ruled out. This matter has been discussed in detail.

Clinically, most of the patients observed had a typical form of amyotrophic lateral sclerosis, although two of the patients on Guam also had evidence of parkinsonism. The possibility that there might be an association between amyotrophic lateral sclerosis and some form of encephalitis is considered, but there is still little evidence for such a relationship.

Clinical laboratory tests were principally of value in ruling out other conditions. A small proportion of the patients had positive blood Kahn reactions, but spinal fluid reactions were negative.

Muscle biopsies showed chronic muscle atrophy. Necropsy specimens showed findings which were consistent with the diagnosis of amyotrophic lateral sclerosis.

On the basis of statistical studies made for many parts of the world, the geographic distribution, with the exception of the Mariana Islands, appears to be uniform and the disease relatively rare. On Guam and Rota, however, the prevalence ratio (about 200 per 100,000 population) is at least 50 times that of the rest of the world from which reports are available. As in the classic form of the disease, males were affected twice as often as females.

On Guam, incidence and mortality from amyotrophic lateral sclerosis are also about 50 times as high as reported elsewhere.

Age distribution is similar to that of typical amyotrophic lateral sclerosis as reported by others. The mean age is 44 years, the range is 20 to 69 years.

On the basis of death certificates dating back to 1904, it appears that amyotrophic lateral sclerosis is not a new disease on Guam. It is suggested that the disease originated or has selectively persisted among the people of Umatac. If it originated or was introduced into the population of Umatac it may have spread to the rest of the island from this source.

At the present time, about 4 per cent of all deaths and 8 to 10 per cent of adult deaths on Guam are due to amyotrophic lateral sclerosis.

Survival rates of the patients were calculated. The median survival period after onset for the entire group was 3.0 years. There was no difference in these rates for the two sexes; patients in whom the disease developed at a younger age had a longer survival time than those in whom it developed at older ages.

These findings indicate that amyotrophic lateral sclerosis is highly endemic on Guam and Rota. The need for further study of this unusual situation is evident. It is hoped that studies which are now under way will clarify some of the questions which have been raised in this report.

APPENDIX 1

ESTIMATION OF PREVALENCE IN THE UNITED STATES AND CANADA

1. *Mortality Statistical Analysis.* As no suitable estimates of prevalence, geographic distribution, race and sex ratios for amyotrophic lateral sclerosis in any large area were available, it seemed desirable to obtain such values from mortality statistics. The latest mortality data which were available, those for the United States in 1949 and 1950, for the Hawaiian Islands in 1950, for England and Wales in 1951 and 1952, and for Canada and Norway in 1951 were studied.

APPENDIX TABLE 1

MORTALITY STATISTICS FOR RUBRIC 356 (MOTOR NEURONE DISEASE AND MUSCULAR ATROPHY), UNITED STATES, 1950*

Rubric 356: Motor neurone disease and muscular atrophy	*All races*		*White*				*Nonwhite*			
	Both sexes		*Male*		*Female*		*Male*		*Female*	
	Number	*Rate†*	*Number*	*Rate†*	*Number*	*Rate†*	*Number*	*Rate†*	*Number*	*Rate†*
.0 Progressive muscular atrophy	317	0.2	178	0.3	120	0.2	11	0.1	8	0.1
.1 Amyotrophic lateral sclerosis	667	0.4	408	0.6	228	0.3	18	0.2	13	0.2
.2 Spinal type of muscular atrophy (includes Werdnig-Hoffmann, Charcot-Marie-Tooth, and so forth)	19	‡	11	‡	5	‡	3	‡	0	0
.3 Other and unspecified manifestations	3	‡	2	‡	1	‡	0	0	0	0
Total	1,006	0.7	599	0.9	354	0.5	32	0.4	21	0.3

Male to female ratio for rubrics 356.0 and 356.1 combined is 1.8 to 1.0.

*—Vital Statistics—Special Reports—National Summaries—Deaths and crude death rates of each cause by race and sex, U. S. 1950. Vol. 37, No. 6, p. 128, of February 16, 1953.

†—Rate per 100,000 population.

‡—Less than 0.05 per 100,000 population.

Appendix table 1 represents values for the United States in 1950. Groups 356.0 (progressive muscular atrophy) and 356.1 (amyotrophic lateral sclerosis) are of particular interest in the present study. It will be noted that the reported nonwhite rate is less than the white rate. (It is not certain whether this is a real difference or is due to differences in medical care for the races or to the failure of some physicians to differentiate amyotrophic lateral sclerosis from central nervous system syphilis in the nonwhites). The male to female ratio is about 1.8 to 1.0.

For 1949, it was possible to obtain the number of deaths by regions in the United States. The numbers and total rates by regions for rubrics 356.0 (progressive muscular atrophy) and 356.1 (amyotrophic lateral sclerosis) are combined in appendix table 2. The three deaths in Hawaii in 1950 are included in this table.

APPENDIX TABLE 2

DEATHS AND DEATH RATES PER 100,000 POPULATION FOR PROGRESSIVE MUSCULAR ATROPHY AND AMYOTROPHIC LATERAL SCLEROSIS IN THE UNITED STATES, BY REGIONS, 1949*

	Number	*Rate per 100,000 population*
United States		
Total	1,004	0.67
Region		
New England	72	0.8
North Atlantic	214	0.7
East North Central	238	0.8
West North Central	101	0.7
South Atlantic	104	0.5
East South Central	58	0.5
West South Central	82	0.6
Mountain	25	0.5
Pacific	110	0.8
The Hawaiian Islands (1950) (population 544,000)	3	0.6

*—Compiled from data supplied by the National Office of Vital Statistics, Public Health Service, Department of Health, Education, and Welfare, Washington 25, D. C., July 10, 1953.

Little significance can be given to the regional differences noted for such mortality statistics. The values in the South particularly are lower than in other regions but adjustments for the lower nonwhite rate and the lower age composition of the population in this area would have the effect of approximating these values to those of the more northern regions.

In Canada, it was possible to examine all the death certificates in the rubric 356 (appendix table 3). The death rate per 100,000 for Canada is 0.81 if it is computed in the same manner as that for the United States. However, it was possible to review each of the Canadian death certificates, and only those terms which were considered acceptable as a form of amyotrophic lateral sclerosis, progressive muscular atrophy, primary lateral sclerosis, or progressive bulbar palsy were included in a "corrected terminology" list. When this

APPENDIX TABLE 3

DEATHS FROM PROGRESSIVE MUSCULAR ATROPHY AND AMYOTROPHIC LATERAL SCLEROSIS IN CANADA, 1951

Rubric	*Male*	*Female*	*Total*
356.0 (Progressive muscular atrophy)	35	24	59
356.1 (Amyotrophic lateral sclerosis)	33	21	54
Total	68	45	113
Rate per 100,000 population*	0.96	0.65	0.81

Ratio male to female: 1.5

*—Canadian population—1951 figures—World Almanac 1953, p. 326.

was done, nine of the original 113 death certificates were excluded, since the condition reported was apparently due to some form of acute vascular accident. This left 104 deaths. However, it was possible, owing to the unique statistical tabulating system adopted in Canada, to determine the number of deaths in which amyotrophic lateral sclerosis had also been listed as a "secondary," that is, complicating or contributory, cause of death. An additional 21 deaths in this category were thus added, raising the total Canadian deaths in 1951 to 125. The 125 "terminology corrected" deaths are believed to present a more accurate and complete accounting of all amyotrophic lateral sclerosis deaths than that provided in the 113 "primary" tabulated deaths for Canada. The "corrected" Canadian death rate is thus $\frac{125}{113} \times 0.81$ or 0.89 per 100,000 population.

The same corrective steps could not be carried out for the United States deaths in this category, since the number of "secondary" causes of death could not be determined. However, if we assume that the same degree of error in terminology and "secondary" deaths occurs in the United States as in Canada, a "corrected" death rate, reached by applying the Canadian correction factor (that is, $\frac{125}{113} \times$ reported death rate) can be determined. For the United States, this becomes 0.67 per 100,000 $\times \frac{125}{113}$ or 0.74 per 100,000 population. The total rate for the United States and Canada combined is taken as 0.8 per 100,000 population.

APPENDIX TABLE 4

MORTALITY STATISTICS FOR RUBRICS 356.0 (PROGRESSIVE MUSCULAR ATROPHY) AND 356.1 (AMYOTROPHIC LATERAL SCLEROSIS) FOR ENGLAND AND WALES* AND FOR SCOTLAND, 1952

	England and Wales						*Scotland*					
	Both sexes		*Male*		*Female*		*Both sexes*		*Male*		*Female*	
	Number	*Rate†*	*Number*	*Rate†*	*Number*	*Rate†*	*Number*	*Rate†*	*Number*	*Rate†*	*Number*	*Rate†*
Rubric 356.0..356	0.8	208	1.0	148	0.6	31	0.6	24	0.9	7	0.3
Rubric 356.1..120	0.3	83	0.4	37	0.2	19	0.4	10	0.4	9	0.4
Total 476	1.1	291	1.4	185	0.8	50	1.0	34	1.3	16	0.6
	Ratio male to female: 1.8						Ratio male to female: 2.1					

*—The 1951 rates for England and Wales were available but are not included since they were similar to the 1952 rates.

†—Rate per 100,000 population.

Sources: Personal communication from the Registrar General, General Register Office, London, November 26, 1953.
Personal communication from the Registrar-General, New Register House, Edinburgh, December 9, 1953.

In Great Britain, deaths reported as due to "progressive muscular atrophy" are two to three times more frequent than those reported as "amyotrophic lateral sclerosis" (appendix table 4), whereas in the United States "amyotrophic lateral sclerosis" deaths are twice as frequent as deaths due to "progressive muscular atrophy" (appendix table 1); and in Canada and also in

APPENDIX TABLE 5

MORTALITY STATISTICS FOR RUBRICS 356.0 (PROGRESSIVE MUSCULAR ATROPHY) AND 356.1 (AMYOTROPHIC LATERAL SCLEROSIS) FOR NORWAY, 1951

	Both sexes		*Male*		*Female*	
	Number	*Rate**	*Number*	*Rate**	*Number*	*Rate**
Rubric 356.0	17	0.5	9	0.6	8	0.5
Rubric 356.1	12	0.4	9	0.6	3	0.2
Total	29	0.9	18	1.2	11	0.7
Ratio male to female: 1.7						

*—Rate per 100,000 population.

Source: Personal communication from Dr. Knut B. Westlund, Department of Health, Government of Norway, November 28, 1953.

Norway (appendix tables 3 and 5) the two are about equal. This may represent variations in local usage of the terms; until a sample of the patients and the certificates themselves can be examined, the reason for this discrepancy will not be clear.

As in the United States and Canada, the ratio of males to females for progressive muscular atrophy and amyotrophic lateral sclerosis combined in Scotland, England, Wales, and Norway approximates two to one. The total rates for the "primary" causes only in England and Wales and in Scotland of 1.0 and in Norway of 0.9 are slightly higher than those for the United States (0.7) and for Canada (0.8). However, adjustment for age differences in the populations involved would tend to decrease the difference. For the purpose of the present report, it is apparent that amyotrophic lateral sclerosis and progressive muscular atrophy in all these countries are relatively rare causes of death.

The average duration of amyotrophic lateral sclerosis is reported as about three years. An approximation of the prevalence rate may be made for a disease such as amyotrophic lateral sclerosis, which is almost always fatal, by multiplying the mortality rate by "average duration" in years. For amyotrophic lateral sclerosis in the United States (including Hawaii), Canada, Norway, England and Wales this would be about 0.9×3 or 2.7 per 100,000 population.

2. *Prevalence in Rochester, Minnesota.* An examination of Mayo Clinic records indexed as amyotrophic lateral sclerosis, progressive muscular atrophy, or progressive bulbar palsy for the period 1948 to 1952 for residents of Rochester, Minnesota, and the immediately surrounding area (total population about 33,000) was carried out. It is believed that this source provides information about most, if not all, Rochester resident cases. Three local resident cases diagnosed during this five year period were found. One patient had died in 1949, and two were living on August 1, 1953. One was a lifelong resident of the area; the other had moved to Rochester three years previously, just after the time of onset of her symptoms.

On the basis of this small sample, the prevalence rate would be about six per 100,000 population.

For the purpose of our study, an "expected" rate of four per 100,000 population is adopted.

APPENDIX 2

The natives of Guam are predominantly a mixture of three racial groups, the Filipino, the Spanish, and the original Chamorro strain. When Magellan discovered Guam in 1521, it was estimated that there were approximately 70,000 Chamorros on the Mariana Islands. The Spaniards finally subdued the islands about 1700. The total native population was then estimated at 1,654. The vast majority of these were women and, except for a few family groups who hid on the Island of Rota, they were moved to Guam. An infusion of Spanish and Filipino blood helped to save the Chamorros from extinction. Offspring of native women and foreign soldiers soon began to outnumber the true Chamorro group. In spite of this, the total population never again much exceeded 5,000 until the twentieth century. There has been little if any infusion of new blood since the nineteenth century. It has been assumed that the natives of Rota carry the purest strain of Chamorro blood, although the natives of the more isolated southern part of Guam may also represent a purer strain of Chamorro than those of other parts of Guam. In this regard, it is of interest that the relatively isolated populations of Rota and Umatac speak Chamorron with a unique singsong quality that distinguishes them from other Chamorros.

APPENDIX 3

COPY OF DEATH CERTIFICATE — GUAM

762[a]

FELIX TENORIO TORRES
Agana
1° de Novembre de 1904
L.4, f. 153

El Gobernadoreillo de Agana dio cuenta con fecha de hoy de que en la Cabecera de su cargo fallecio, el dia de ayer, treinta y uno de Octubre, a consecuencia de un "progresive muscular atrophy," FELIX TENORIO TORRES, de cuarenta y siete anos de edad y vecino de dicha Cabecera. Agana, primero de Novembre de mil novecientos cuatro. Raymond Stone.

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In 1857, Sir C. Locock introduced the use of Bromide of Potassium for the treatment of catamenial epilepsy in the following remarks at a meeting of the Medico-Chirurgical Society. "There is a form of epilepsy to which special notice has not been drawn, and which I have been in the habit of regarding as hysterical epilepsy. It is confined to women, and observes a regular return connected with the menstruation. It is as baffling a form of epilepsy as any other. The paroxysms only occur (except in the case of great mental excitement) at the menstrual period. Having been often baffled in these cases, of which I have seen a considerable number, I have been led within the last twelve months to try a remedy which has so far answered my expectations that I think it desirable it should have a larger trial by being made known to a larger number of persons." He then related the particulars of a case of this kind which had been cured by ten-grain doses of the bromide given three times a day and continued for some months, and added – "I have tried the remedy in fourteen or fifteen cases (all under thirty) and it has only failed in one."

W. R. Gowers in *Epilepsy and Other Chronic Convulsive Diseases*, published in 1885.

TREATMENT REVIEW

This section is designed to give prompt publication to the results of reliable studies in therapy, to record newer methods of treatment, and to encourage research in therapy of neurologic disorders.

AUGUSTUS S. ROSE, M.D., *Section Editor*

TETANUS

Historical Review of Treatment

Arthur L. Drew, M.D.

"An inhuman calamity! An unseemly sight! A spectacle painful even to the beholder! An incurable malady! Owing to the distortion, not to be recognized by the dearest friends. And hence the prayer of the spectators, which formerly would have been reckoned, not pious, now becomes good, that the patient may depart from life, as being a deliverance from the pain and unseemly evils attended on it. But neither can the physician, though present and looking on, furnish any assistance, in regard to life, relief from pain or from deformity. – With them, then, for overpowered by this disease, he can merely sympathize. This is the great misfortune of the physician." – ARETAEUS THE CAPPADOCIAN.[1]

THE HISTORY of the clinical syndrome, the etiologic studies and speculations culminating in discovery of the organism, and the final striking demonstration that the human clinical tetanus is almost entirely preventable, is a fascinating story that in many ways parallels the development of modern medicine.

The dramatic effectiveness of tetanus toxoid prophylaxis is apparent from the records of World War II. Long and Sartwell[2] reported only one case of tetanus in 160,254 battle-wounded Army personnel during the second World War. During the entire war period only 12 cases of tetanus occurred in the Army. There were five deaths, only two of which had received the proper emergency stimulating dose of toxoid. This mortality rate of 0.02 per 100,000 per year compares dramatically with the civilian mortality rate in comparable age groups during the preceding four year period. This civilian mortality rate was 0.41 per 100,000 per year or 20 times higher.[2]

The figures reported by Boyd on tetanus in the British forces are almost as favorable.[3] He reported only 19 cases of tetanus in a group of 289,649 immunized battle wounded.

Despite the fact that immunization by means of toxoid appears capable of reducing human tetanus to the category of a rare disease, the civilian mortality rate in the United States for 1948 was 0.3 per 100,000.[4] This figure indicates that recognized preventive measures have not been utilized to their fullest extent. As a result, current medical literature continues to carry frequent ref-

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erences to the treatment and management of human clinical tetanus, a disease which has changed little since the time of Aretaeus of the first century.[1] Its treatment and management continues to be a serious and complex problem.

Tetanus was known and described by Hippocrates[5] and it seems highly unlikely that such a dramatic syndrome was unknown to his predecessors. From antiquity until the discovery of the *Clostridium tetani*, the literature is replete with descriptions of the disease and surmises as to etiology. Many empirical remedies were suggested, and in 1861 Hughlings Jackson[6] summed up the attitude of the era prior to the discovery of the organism in 1884 by Nicolaier.[7] Jackson wrote, "Although we cannot as yet point to any special plan of medication, and say that it has proved to be the best, certain broad rules for our guidance have been established, and even very severe cases who every now and then get well, is an undoubted fact." Reference to the Index Catalog of the Library of the Surgeon's Generals Office for this period[8] sheds considerable light on the "pre-scientific" treatment of tetanus. Cases in which "cures" were achieved by the application of ice to the spine are followed by an equal number of therapeutic successes due to immersion in hot baths. Arsenic, tincture of cantharides, strychnine, musk, hashish, purgation, antimony, mercury, "the liberal use of wine," serpent venom, carbonate of ammonia, jalop, aconite, nicotine, tincture of rhubarb, and acupuncture were all advocated. It is obvious that the management of tetanus was poorly understood. The use of opium, chloroform, and ether appears more rational to present day practitioners, but even these agents were not always used on the basis of any real understanding of the disease.

During the period that the above therapeutic methods were being tried empirically, many developments in the bacteriologic field were taking place. According to von Lingalsheim,[9] Michaelis in 1797 was the first to suggest that the symptoms of tetanus might be due to the irritation of the peripheral nerves by secretions of certain nerves. Thriar[10] credits Dufouart with writing in 1801 that the symptoms might be due to an infective virus. Simpson[11] was probably the first to suggest that a poison was generated at the site of the wound. Many attempts at artificial transfer were made prior to the successful experiment performed by Carle and Rattone in 1884.[12] The year 1884 was rounded out by Nicolaier's identification of the organism in mixed cultures.[7] It was not until five years later that Kitasato[13] was able to obtain a pure culture with which clinical tetanus could be produced. He suggested that the symptoms were due to a poison absorbed from a local area of infection. Faber[14] was able to confirm this thesis by the production of tetanus with germ-free filtrates. Within a year von Behring and Kitasato[15] demonstrated that immunization was possible. It is interesting to note that, according to Humphreys,[16] this work led not only to the ultimate development of tetanus antitoxin, but also formed the basis for all practical applications of serum therapy.

Humphreys[16] summarized the characteristics of the organism as follows: "It has generally been considered that those anaerobic rods with round terminal spores that are capable of producing the characteristic neurotoxin form a rather exceptionally well defined group, the members of which vary only slightly one from the other. Although from a practical medical point of view this conception still holds good, modern study is making it increasingly apparent that the limits of *Clostridium tetani* as a botanical species are by no means so clearcut. On the one hand, certain varieties exist, which though highly toxic, differ from

the accepted species-type in morphology, motility, and biochemical activities; while, on the other hand, non-toxic variants occur, which may or may not agglutinate with one or another of the known tetanus agglutinating serums, but which appear otherwise, morphologically and biologically, to be identical with the usual forms." From a practical point of view, formation of a toxin which produces the characteristic symptoms and is specifically neutralizable by tetanus antitoxin is sufficient to include an organism within the species of *Clostridium tetani*.

A number of workers have confirmed and extended the original observation made by Tulloch[17] that distinct serologic types of tetanus can be differentiated. According to Humphreys nine agglutinative types have been described.[16] All of these types produce the same, if any, toxin, which can be neutralized by the identical antitoxin.

Several points of interest arise concerning the resistance of tetanus spores. It appears likely that different strains of *Cl. tetani* produce spores of varying degrees of resistance to heat and other noxious agents, but in addition the same strain may have mature spores which vary in resistance depending upon the culture medium. Furthermore, the same strain in the same culture may produce individual spores with increased heat tolerance, as well as delayed germination. The organisms, or rather the spores, have been found almost universally in the soil, as well as in the dejecta of man and many domestic and wild herbivorous animals.

In reviewing the characteristics of the organism and its spores, the great variability in spore resistance, toxicity, serologic type, and strain is impressive. An awareness of these characteristics may aid in understanding some of the discrepancies reported in the literature regarding treatment, clinical variants, morbidity and mortality differences, as well as the differences of opinion and fact concerning the basic pathophysiology of clinical tetanus.

More pertinent to a discussion of the problems of clinical human tetanus is the consideration of the characteristics of tetanus toxin itself. Actually there are two exotoxins produced by *Clostridium tetani*. These distinct and very different toxins were first separated by Ehrlich.[18] They are apparently formed independently, but are both antigenic and physiologically active. Tetanospasmin, the more important, is the neurotoxin considered responsible for the symptoms of tetanus. The other exotoxin, known as tetanolysin, is a hemotoxin capable of destroying red blood cells and possibly leukocytes. It has been shown that nonpathogenic strains of tetanus bacillus produce no tetanospasmin but form only the tetanolysin.[19,20] Fildes[21] believed that, while tetanolysin is nonpathogenic, it may promote the tetanus infection by virtue of its possible antiphagocytic action. It is also conceivable that tetanolysin may play a part in some of the phenomena of "local" and "chronic" tetanus.

The pathogenic tetanus toxin, tetanospasmin, is one of the most powerful poisons known. It is virtually inert except by the parenteral route, extremely labile, and easily destroyed by a variety of physical and chemical agents. Toxin production is markedly altered by the symbiotic organisms comprising a mixed culture such as may occur in a wound.

Important in evaluating experimental studies in the pathogenesis of tetanus is the recognition of the wide species variability in susceptibility to tetanus toxin. Man and the horse appear to be among the most susceptible, while some other animals are quite resistant to infection. The exact reason for these variations in susceptibility appears unknown.

According to Abel and Hampil,[22] it was Curling[23] who first clearly stated the

position that tetanus is a disease of the central nervous system only. Curling indicated that Galen and others had previously expressed similar ideas. Curling conceived of tetanus as a disease unaccompanied by any perceptible lesions of structure, the nature of which, although essentially distinct from inflammation, was completely unknown. Although many pathologic findings have been reported from time to time, there is rather general agreement that these changes are toxic and reversible.[24–26] Wilson[27] pointed out "that none of the reputed changes can be specific for tetanus, each and all being seen in a host of toxic and infective states."

There is considerably less agreement as to the pathophysiology of tetanus. The absence of demonstrable pathologic changes in tetanus, together with certain observations in local tetanus, has stimulated a great deal of opposition to the concept of tetanus as a disease of the nervous system alone. Curling[23] clearly believed that the symptoms of tetanus were due solely to continued "tetanic irritation" of the motor system and that continued stimulation led to permanent contractures. This aspect of the central neural hypothesis, together with the manner of tetanus toxin transport to the central nervous system, requires further discussion. A number of clinical and experimental facts cast doubt on the thesis that all the phenomena observed can be explained on a central basis. Abel[28] pointed out, "Certain of its symptoms, however, as the so-called local tetanus and the long continued rigid states of certain muscles . . . cannot be brought into line with this concise definition of the disease." Ranson[29–32] suggested that the toxin acts directly on muscle, as well as on the central nervous system. He and his co-workers reported histologic changes in the muscle of animals with local tetanus, and surmised that the sarcoplasm is changed by the toxin to an irreversible gel. In this connection Florey and his associates[33] were unable to abolish completely with curare, the "rigidity" of local tetanus in experimental animals, and they speculated that "actual changes in the muscle were now responsible for some of the rigidity."

Heiberg[34] asserted that tetanus was not a nervous disease but a disease of the blood which localized itself in the muscles. He believed that local tetanus was quite independent of central influence and was due to the direct action of the toxin on the muscles themselves which degenerated and, as a consequence, shortened. Rose[35] described cephalic tetanus, and according to Abel and Hampil,[22] should be given credit for stressing the fact that reflex excitability and convulsions were late manifestations of the disease. He described ". . . tetanus, in its true form, as a disease that manifests itself in its first stage as muscular rigidity and then passes on to a third state with tonic jerks which may become chronic. . . . " Abel and Hampil felt that Rose came to an unsound final conclusion in his statement that tetanus is a disease involving the central nervous system alone. Many writers have not been entirely satisfied with a purely central explanation of the clinical findings.[22,28] Observations in local tetanus and head tetanus are difficult to explain on a theory of central action alone. Some have seen the clinical manifestations of tetanus as a combination of both local peripheral and central action but believed that the local action was only a prerequisite to the appearance of the final central action.

A number of ingenious and ingenuous theories have been proposed in an attempt to reconcile these apparently divergent clinical and experimental facts. Abel[28] has reviewed the major hypotheses and found that, "Four different theories have been proposed to explain local tetanus, and four more have been de-

vised to show the pathways by which the toxin reaches the central nervous system."

Meyer and Ransom[36] and Marie and Morax[37] represent the school which insists that the toxin is transported to the central nervous system by way of the axis cylinder of motor nerves. Variations of this theory include the thesis that the toxin reaches the central nervous system by way of endoneural and perineural tissue spaces. A third variant of the neural transport theory is that the toxin is absorbed by the terminals of mixed nerves and transported to the cord and brain by way of tissue spaces of the nerve. Abel and his co-workers[28,38,39] have, on the basis of series of experimental studies, come to the conclusion that the toxin "can be carried to the various tissues of the body, including those of the central nervous system, only by way of the arterial blood stream," and they stated categorically that tetanus toxin is not carried to the central nervous system by any component of the peripheral nerve.

However, Friedemann and co-workers[40–42] reopened the controversy and attempted to go back to the theory of neural transport in stating that tetanus toxin reaches the central nervous system via the motor nerves and spreads within the central nervous system. They conclude that their ". . . experiments . . . confirm the nerve . . . carriage theory of Meyer and Ransom in all essential points." Friedemann also stated that "local tetanus is of central origin."

Several interesting attempts to explain the phenomena of local tetanus have been made. Abel, Firor, and Chalian[43] stated that "the toxin exhibits both a central and peripheral action, each of which may be demonstrated independently of the other. The central effect, which is characterized by reflex motor convulsions, is due to the poisoning of the motor nerve cells of the spinal cord, medulla, and pons; the peripheral effect, recognized as the unremitting rigidity of voluntary muscles, results from the fixation of the toxin upon the motor end organs."

Other attempts to explain all the observed facts have led to the postulation of a two-fold action of the toxin. As long ago as 1899, Courmont and Doyon[44] postulated that stimulation of the sensory nerve endings by the toxin with the production of local tetanus, resulted in elaboration of a secondary toxic substance which was transmitted via the blood stream to the central nervous system and thus caused the symptoms of generalized tetanus. Harvey[45] and Bayne-Jones[46] have suggested that the toxin destroys acetylcholinesterase, with a resultant increase in acetylcholine leading to increased muscle irritability.

No reference to the fact that there are two types of tetanus exotoxin, tetanospasmin and the so-called tetanolysin, has been found. It is interesting to speculate as to the part the latter might play in the production of some of the phenomena of local tetanus, as well as the chronic muscle rigidity seen clinically. It seems at least theoretically possible that tetanolysin might be a factor in producing local muscle changes such as have been described by Ransom[29] and postulated by other workers.[38]

Despite additional observations concerning the pathophysiology of human tetanus made possible by the use of newer therapeutic agents such as myanesin and the curares, there still remains much to be explained before an acceptable theory of pathogenesis is achieved. At the present time no single theory of the pathogenesis of tetanus is completely tenable. This adds to the confusion and general disagreement regarding proper clinical management of human tetanus. Until such time as a pathogenic theory is proved and accepted, the therapy of human clinical tetanus will remain em-

pirical and thus subject to constant re-evaluation.

TREATMENT

ANTITOXIN AND SURGERY

The period of rational treatment of tetanus may be said to have begun with the isolation of the organism and the development of an antitoxin. Von Behring and Kitasato[13,15,47–49] reported the discovery of tetanus antitoxin in a series of papers. Even at this stage, a fundamental difference of opinion arose. Kitasato[49] believed that tetanus antitoxin had definite therapeutic value; but while Roux and Vaillard,[50] Nocard,[51] and Tizzoni and Cattani[52] confirmed the prophylactic value of tetanus antitoxin, they were unable to convince themselves experimentally of its therapeutic efficacy.

The prophylactic value of tetanus antitoxin and tetanus toxoid is now beyond question. However, the therapeutic value of antitoxin can be seriously questioned. As Topley and Wilson[53] stated, "Whether or not antitoxin is of any value in man when given subsequently to the development of tetanus is a question that has received no definite answer."

It is possible to amass a great deal of experimental and clinical data purporting to show the therapeutic efficacy or lack of efficacy of tetanus antitoxin. Sherrington[54] reported that antitoxin was of therapeutic value in monkeys injected with pure toxin, not bacilli. He used doses corresponding to a single human dose of 120,000 units of antitoxin. Firor[55] also reported benefit from the therapeutic use of antitoxin in dogs. Human clinical experience favors the efficacy of tetanus antitoxin as a therapeutic agent, but it should be remembered that deductions drawn from clinical experiences with tetanus are subject to considerable error. Firor pointed out that, if valid statistical comparisons are to be made, certain details of the clinical course must be known. These include the length of incubation, the interval before treatment, severity of symptoms, and other clinical features which unfortunately are frequently lacking in reports in the literature. Further, sufficient experimental data have accrued so that the statement by Abel and Chalian[56] is not readily refuted. These authors summarized their position by stating that ". . . antitetanic serum is powerless to mitigate or to abolish existing and clearly evident symptoms . . . . " and that "serum fails to save life; and it cannot therefore be thought of as having a specific curative action."

However, in human clinical tetanus, a number of uncontrolled variables alter the situation from that of a carefully conducted animal experiment. As Abel and Chalian have pointed out, in man we do not know whether toxin is being elaborated, or at what rate, or in what amount. Further, as Firor[55] noted, we cannot ascertain lethal or sublethal amounts of toxin, or whether a lethal or sublethal dose has been fixed in the nervous system. Lastly, the clinician can hardly solve the problem as to what proportion of toxin is fixed irretrievably and what is only adsorbed to the cell. Abel and his co-workers made this distinction and suggested that the adsorbed portion of the toxin may still be neutralizable.[56,57] Cole and Spooner[58] found some 25 per cent of a single large intravenous dose of antitoxin still demonstrable in the blood seven days after injection. This, together with the work of Ransom,[59] strongly suggests that the toxin-nerve cell union is not readily disrupted by antitoxin. The answer for the clinician has been aptly stated by Abel and Chalian: "We must continue to employ antitetanic serum in all cases of the disease at the earliest possible moment, in order to save that limited number we have every reason to believe can be saved." [56]

Having decided to utilize tetanus antitoxin therapeutically, the much disputed

problem of dosage and route of administration must be met. Whatever has been written concerning the uncontrolled variables in human clinical tetanus is even more pertinent to the problem of dosage and route. It seems more than likely that until such time as statistically valid series, carefully selected and annotated, are collected, no final answer to the dosage and route of administration of tetanus antitoxin can be given.

Cole[60] has proposed a useful clinical classification of tetanus. He delineates four types of cases: 1) local tetanus only; 2) generalized rigidity with slight or absent reflex spasm and irritability; 3) generalized rigidity with marked reflex spasm and irritability, followed by slowly subsiding generalized rigidity; and 4) marked and continuous spasms with hyperpyrexia and death from cardiac or respiratory failure. Certainly any estimate of the efficacy of therapy with antitoxin or any other therapeutic measure must take these clinical characteristics into consideration. Other factors which always influence the therapeutic results regardless of form of therapy are those noted by Firor[55]: length of incubation, interval before treatment is begun, severity of symptoms, location of wound, age of patient, and cardiac or other complicating conditions. Until these factors are presented with careful details of treatment, claims presented by various authors regarding this or that dosage or route of administration of tetanus antitoxin can only be regarded as matters of opinion rather than scientific fact. It has been reported that, with doses of tetanus antitoxin from 30,000 units up, human cases of tetanus have survived.[61] Because the problems of dosage and route of administration are so intimately related, it is necessary to refer to a great mass of reported work. Few if any of these reports enable the reader to ascertain how well controlled were the variables discussed above.

Proponents of the intrathecal route of administration of tetanus antitoxin include Sherrington,[54] Firor,[55] Shumacker, Firor, and Lamont,[62] Ashhurst,[63] Yodh,[64] and Nabarro.[65] Firor, Yodh, and Nabarro urged consideration of the cisternal route for administration. Opposed to intrathecal and cisternal administration of antitoxin are Florey and Fildes[66] who reported no better therapeutic results than those obtained with intravenous administration alone. Paterson,[67] using large doses by intravenous and intramuscular routes, reported an impressive 19 survivals in 26 cases. Wainwright suggests that the best way to reduce mortality is to forbid the use of intraspinal antitoxin. Pratt[61] stated that intrathecal antitoxin "was suggestively, but not definitely, more effective than giving the same amount of antitoxin by the intramuscular or intravenous routes." He also pointed out that fatal reactions to intrathecal administration may occur in patients who would otherwise have survived, and urged that if intrathecal medication is to be used at all, it be given only to the most severe cases. Spaeth[68–70] condemned the intrathecal route on clinical grounds as well as on the basis of studies of the antitoxin titers. Dietrich, Karshner, and Stewart,[71] in referring to the intrathecal and intravenous administration, stated that the "treatments actually killed 11 or 12 of the 13 patients who died." Dietrich[72,73] further stated that "it is my conviction that intramuscular antitoxin is effective and is the safest route of administration in children." He felt that the high early mortality rates reported by Yodh[74] and Smathers and Weed[75] "constitute a convincing argument against intrathecal and intravenous administration of the serum." It would appear that this line of reasoning is as applicable to adult cases as it is to pediatric cases of tetanus. There seems little justification for the intravenous or intrathecal administration of a therapeu-

tic agent whose fundamental efficacy remains unproved. An analysis of tetanus cases in World War I gives added weight to this opinion.[76]

The experiences of Spaeth,[68–70] and Dietrich[73] indicate that initial doses of 10,000 to 30,000 units of antitoxin given intramuscularly and repeated every day for two to four days are as effective as larger doses given over longer periods of time by other routes. The program recommended by Nash, Bryant, and Coller,[77] consisting of 50,000 units intravenously and 50,000 intramuscularly together with 10,000 units infiltrated around the wound and 5,000 units of antitoxin every three or four days, could best be modified by the omission of the intravenous administration. It is otherwise a satisfactory and rational schedule, particularly in those patients with relatively large contaminated wounds where continued production of toxin is anticipated. These authors also recommend wide debridement of the wound with open packing thereof. Zinc peroxide dressings are recommended. This recommendation is not supported by the experimental studies of Coleman[78] who found that surgical cleansing and debridement did not appear to alter the course of the disease. McClintock and Hutchings[79] showed that even as complete a debridement as amputation failed to alter the course of the disease in critical animal experiments. Gowers[80] cited several cases where surgical interference with a wound apparently brought on clinical tetanic symptoms.

There is no question that surgical care of a traumatic wound should always be given. However, surgical procedures should not be considered therapy for the clinical manifestation of tetanus, and there is some evidence that overzealous debridement may increase the systemic release of toxin.

In addition to tetanus antitoxin and surgical debridement of the wound, other methods of treatment of human clinical tetanus are now available. Bearing in mind the lack of specific pathologic change and the fact that even very severe cases every now and then get well,[6] and pausing to consider that the outstanding signs and symptoms of the disease are spasm, rigidity, and convulsions, it is not strange that muscle relaxing agents have been used in its management. Two of these agents, curare and myanesin, will be discussed in some detail. The use of sedation, antibiotics, and tracheotomy in the management of the manifest symptoms of human tetanus will also be considered.

CURARE

Curare, the first of the symptomatic and supportive measures to be considered, has a long and interesting history. McIntyre[81] has reviewed the various facets of the subject. The present discussion is necessarily limited to those details pertinent to the use of curare in the management of tetanus. There is some disagreement as to the earliest mention of curare in European literature. McIntyre credits Pietro Martire d'Anghero, in *De Orbe Novo* of 1516,[82] as the first European author to mention curare. However, others believed that Sir Walter Raleigh deserves credit not only for introducing curare into Europe but also for the first description of its actions.[83,84] Early investigations of the properties of curare and its clinical application were hampered by the difficulties involved in obtaining an adequate and uniform supply of the crude drug. Despite the interest and importance of some of the work done in the nineteenth century, it was not until Gill[85] observed and learned the native method of preparing the crude alkaloid that any real therapeutic application of its properties could be made.

The name of Claude Bernard is intimately associated with the definitive statement of the myoneural action of

curare.[86–88] However, much interesting work had been reported prior to Bernard's papers, and these observations are of particular interest in an historical evaluation of therapy of tetanus.

It is difficult to determine just when the idea of using curare in the treatment of tetanus occurred. According to McIntyre "the earliest therapeutic use of curare was for the control of tetanus." [81] He credited Sewell, a veterinarian, with being the first to use curare in animal tetanus. Following Vella's experience with its use in human tetanus[89–91] there was considerable controversy regarding proper assignment of priority for the idea.[92–95] It appears, however, that the first reported use of curare as a therapeutic agent in human tetanus was that of Burrall.[96] This work attracted little if any notice when published and it remained for Vella to attract real attention to the subject.[89–91]

Shortly, other reports began to appear in the literature.[97–105] An unsigned editorial comment in *The Lancet*[106] in 1859 summed up the opinion regarding the use of curare and epitomized some of the problems arising from its use:

"The successful termination of two cases of tetanus in which curare was employed by M. Vella and M. Chassaignac, has led to repeated trials and as many failures with this potent substance. We may count in all, now, nine attempts and seven failures. Great interest has been excited by the experimental employment of curare in these cases; for the disease is no less horrible than the remedy is heroic. . . . It is one of the least promising characteristics of curare, that both in composition and effect it is uncertain and varying. Its chemical nature is not uniform, even its source is variable, and its energies are unequal in various specimens. This constitutes a great posological objection to its use in its present form. If it were possible to distil a yet more deadly poison from this most poisonous drug, and to extract from it *curarina* as its active alkaloid, a fixed intensity might be attained. The therapeutic effect of curare is unreliable; it cures rarely but it can kill promptly. It was not thought to be poisonous when taken into the stomach; subsequent experiments have proved this to be an error. Experiments upon large animals have shown that after the tetanic spasms have ceased, perhaps controlled by the action of the curare, death has followed apparently from paralysis of the organs of respiration. So that the surgeon has the satisfaction of thinking that if he saves his patient from the disease, he may kill him by the remedy. . . . All this leads us to coincide in opinion with M. Velpeau, who condemns, rather than with M. Bernard, who applauds, curare. . . . What has been done hitherto was justified by the success of Vella and Chassaignac; the subsequent failures suggest the possibility that those were recoveries, not cures."

Gowers, writing in 1900, stated that curare "appears only to avert death from spasm by bringing the patient equally near to death from paralysis."[80] Broca expressed a somewhat more modern and optimistic point of view in his statement: "I do not wish to say that curare should be considered as a specific method of combatting the cause of tetanus; but in paralysing the nerve endings, it can protect the muscular contractions . . . and thus prolong the life of the patient as well as his natural well-being in a disease in which the contractions are only a symptom." [93]

The difficulties of procuring any form of curare and the complete lack of standardization of the drug prevented further therapeutic attempts. Hoffman,[107] Hoche,[108] Symes,[109] and Hunter[110] were among the last to attempt the clinical use of curare in human tetanus until the work of the last two decades. It was not until the work of King[111] and Wintersteiner and Dutcher[112] that purified tubocurarine became readily available. Gill's[85] explorations made these developments possible.

The modern management of human clinical tetanus with curare began with the work of Florey, Harding, and Fildes,[33] Cole,[113] Mitchell,[114] and West.[115] Florey and his co-workers reported that it was possible to abolish local rigidity with a

sufficiently large dose in experimental tetanus of rabbits. Further they pointed out that "in animals in which local tetanus has been present for some days, curarine was found to be only partially capable of abolishing the rigidity, but had a definite effect. It is likely that actual changes in the muscle were now responsible for some of the rigidity." They also made one of the most lucid statements of the outstanding characteristic, or peculiarity, of human clinical tetanus. The thought is not original and has often been expressed, but is well worth emphasizing. "If a person recovers from tetanus he recovers completely . . ." This means that the toxin can be eliminated completely and leave the nerve-cells intact. Antitoxin, even in a very large dose is apparently incapable of removing toxin already fixed to the nerve-cells, but the toxin is probably oxidized slowly. If the patient can be saved from exhaustion by prolonged spasms and kept supplied with a sufficiency of water and foodstuffs, it should be possible to keep him alive long enough to enable this oxidation to occur." Florey and his co-workers considered two methods of accomplishing this end, prolonged anesthesia and curare.

Mitchell[114] reported a case treated by subcutaneous injection of curare with subsequent recovery. West[115] was also an early worker with this form of treatment. Isacson and Swenson[116] and Cole[113] used the aqueous preparation and, although their patients did not survive, they were convinced of the potential value of curare. Hanna[117] lost his patient, but noted that curare "gave quick and efficient muscle relaxation." The use of the potent and fast-acting aqueous preparation resulted in a number of serious complications. Review of some of these cases strongly suggests that respiratory paralysis was the immediate cause of death. Thus, although promising since the early part of the nineteenth century, curare still did not appear to have practical clinical value in the treatment of human tetanus. At least some of the objections made by Gowers[80] and the unknown *Lancet* editorialist[106] appeared to be still valid. Unfortunately, the generally held belief among clinicians has been that curare either paralyzed or else was ineffective. With the gradual closing of the gap between pharmacologic and neurophysiologic knowledge and its clinical application, curare has come to be a valuable therapeutic agent.

Despite the fact that pharmacologists and neurophysiologists have worked with the drug since 1757,[118] the site and mode of action is still not entirely agreed upon. McIntyre has reviewed the subject intensively,[81] but the evidence brought forward by him does not demonstrate beyond doubt that curare has any action other than at the myoneural junction. Khune[119] described morphologic changes in the end plate itself following curarization, although King and Willard[120] were unable to confirm this earlier observation. It remained for Eccles and Kuffler,[121–125] in a series of beautifully executed experiments, to develop what appears to be the best working hypothesis of curare action and the theory most pertinent to the use of curare in the treatment of tetanus. They have suggested that the myoneural junction can best be considered as a membrane capable of depolarization with a resulting electrical potential. Such a potential can be produced by constant current pulses or by drug stimulation. The magnitude of this potential depends, to some extent, upon the strength of the applied stimulus. A variable degree of control is exercised over the size of the evoked potential. End plate potentials will normally attain a critical level which results in a propagated muscle response. Subcritical potentials, the result of incomplete depolarization of the membrane, lead to

more purely local responses. Experimentally incomplete depolarization, subcritical potentials, and purely local responses can be demonstrated in partially curarized preparations.[125]

These findings suggest a physiologic basis for the so-called *Wedensky Phenomena*,[126] in which it is observed that after a period of time a preparation will fail to respond to a given frequency of repetitive constant current pulses but will continue to respond to all other frequencies of the same pulse. Bremer and Titeca[127] have stated that " . . . slow curarization . . . realizes the condition permitting the inhibition of Wedensky."

Many workers[83,127–133] have noted that subparalytic doses of curare decrease or abolish abnormal neuromuscular responses. The work of Eccles, Kuffler, and co-workers[121–125] appears to give a sound physiologic explanation for this ability of curare to act as a differential screen at the myoneural junction, permitting normal impulses to pass and blocking frequencies outside normal range or duration. It is precisely this differential blocking action of curare which can be utilized in the treatment of tetanus and other conditions accompanied by abnormal muscle tone and hyperirritability. It should be stressed that curarization to the point of paralysis is neither necessary nor desirable in achieving this differential blocking action. Thus, one of the major objections to its use, the danger of respiratory paralysis, can be largely overcome. In order to accomplish this end, however, some method of maintaining curare at steady, almost continual, subparalytic levels is needed. The application of the Romansky[134] method of prolonging intramuscular drug action to curare administration was first reported by Schlesinger in 1946.[130] Further modification of the depot form of curare has materially increased the value of this mode of administration.

Weed, Purvis, and Warnke[135] and Binger and Devnick[136] reported the effective use of the depot form, stating that not only was it of value in controlling tetanic symptoms, but it was not especially dangerous. Adriani and Ochsner[137] and Goodman and Reinhardt[138] stressed the short action of the aqueous preparation and the relative difficulties encountered in preventing overdosage, and have advised against the use of curare in the treatment of tetanus. Schmidt and his associates[139] stated that "curarization would seem to approach the ideal, providing the effect can be controlled satisfactorily." They reported the use of electromyographic studies as a means of achieving this control. There is, at the present time, a growing body of evidence that curare, either in the aqueous form or in the longer-acting depot form, is of great value in management of tetanus.[33,110,113–117,137,139–148]

The possibility of respiratory paralysis has been stressed as a contraindication or at best a severe limitation to the clinical use of curare. Dietrich[72] stated that "Curare (preferably as d-tubocurarine chloride U.S.P. in wax and oil) admittedly results in good muscular relaxation; its use, however, is accompanied with respiratory and other still incomprehensible dangers." Others apparently agree with this appraisal of the use of curare in the management of tetanus.[137,138,149–151] This estimate of a valuable therapeutic agent can only be considered the direct result of failure to appreciate the implications of the work done by Eccles and Kuffler,[121–125] West,[83] Bremer and Titeca,[127] and others,[129–133] and the concept of the subparalytic or "lissive" action of curare. It must be stressed that curarization to the point of paralysis is neither necessary nor desirable in the management of tetanic spasm. In the management of tetanus "we do not . . . attempt to paralyze the myoneural junction, but . . . create a block to certain frequencies imposed on the myoneural

junction by the disease process." [147] Graphic demonstration of these principles applied to tetanus can be seen in the case reports and electromyographic reports of Schmidt and his associates.[139]

If these optimal conditions are exceeded, the antidotal effect of Prostigmine may be utilized,[152–154] always bearing in mind the limitations of such action of this drug[155,156] and the conclusions of Pick and Unna[157] that the central effects of curare and Prostigmine are similar. Positive pressure artificial respiration, endotracheal tube, and tracheotomy, measures which are often required in tetanus itself, give added safeguards in the use of curare.

The observations of Ruskin and coworkers[158] failed to confirm the reported cardiotoxic effects of curare[159] and this complication need no longer be considered in the clinical use of the drug. This is particularly true in curare therapy where the "lissive" effects are desired and lower doses are used.

It appears that d-tubocurarine in the depot form is best adapted to the administration of prolonged subparalytic doses of curare in the treatment of tetanus.[72, 129–131,135,136,147] The aqueous preparation requires more constant surveillance and readily available facilities for positive pressure artificial respiration. The use of the aqueous preparation should be based on the same theoretical considerations as the longer-acting depot form and can be just as effective although somewhat more difficult to use.

McIntyre's statement[81] that ". . . the use of curare in tetanus, when adequate facilities for satisfactory safeguards and competent staff and care are available, should be continued . . ." stresses both the therapeutic value and dangers of this form of treatment. The use of the depot form of curare, according to the principles of incomplete curarization and partial blocking short of paralysis, decreases the dangers of curare in the management of tetanus but does not completely overcome them.

MYANESIN

A newer pharmacologic agent which has proved valuable in the treatment of tetanus is myanesin, an alpha substituted ether of glycerol. Gilbert and Descomp[159] reported some pharmacologic studies on one of the alpha ethers of glycerol in 1910. However, no real clinical interest was shown until the papers of Berger and Bradley[160,161] in 1946 and 1947 in which the action of myanesin was reported. Shortly thereafter Mallinson[162] studied myanesin as an adjunct to anesthesia. Stephen and Chandy[163] investigated the drug in relation to a number of neurologic conditions. The earlier investigators used a 10 per cent solution and noted thrombophlebitis at the site of injection and evidence of hemolyzed blood in the urine. Others [160,161,164,165] also noted hemolytic effects. Schlesinger, Drew, and Wood[166] later reported the uncomplicated and effective use of a 2 per cent solution of myanesin.

Stephen and Chandy[163] had concluded that the drug had little effect on the "transmission of nerve impulses through the synapses of the spinal cord, on conduction of impulses along a nerve, or on transmission of impulses across the myoneural junction." They suggested that the clinical observation of nystagmus and the effect of the drug on some extrapyramidal syndromes pointed to the diencephalon and brain stem as the site of action of the drug. Schlesinger and associates stated the "amelioration of abnormal innervation cannot be attributed to a curare-like myoneural junction effect" and substantially agreed with other investigators that brain stem and spinal cord depression was the determining factor in the action of myanesin.[166] Gammon and Churchill believed that myanesin had a selective action on subcortical nuclei and in increasing doses blocked

the cord next and finally myoneural junction transmission.[167] Finkelman also found the action of the drug was not at the myoneural junction and that much of its effect was exerted on "subcortical efferent pathways." [168]

Berger and Schwartz[169] reported clinical and electromyographic improvement in spastic disorders when the drug was administered by the oral route and stated that prolonged oral administration was without danger. Since then there have been numerous reports on the use of myanesin in a variety of neurologic, psychiatric, and orthopedic conditions.[170–175]

It is difficult to be certain of the earliest treatment of tetanus with myanesin. Gammon[176] reported the beneficial use of myanesin in two cases. Godman and Adriani[177] reported the use of oral myanesin in combination with phenobarbital in their study of various muscle relaxing agents and observed promising results. Moseley and co-workers[178] reported two moderately severe cases of tetanus in which the oral administration of myanesin controlled symptoms adequately. Kahaly and co-workers[179] reported a similar experience in the newborn. Boles and Smith[180] also noted good results with oral administration. A number of others have also reported on the value of myanesin in the management of tetanus.[181–186] The intravenous injection of 25 to 50 cc. of the 2 per cent solution results, in many cases, in dramatic relief of trismus and other "spasms." Electromyographic recordings during this procedure give convincing graphic evidence of reduction of overactivity and a return of the electromyographic record to normal. Similar observations with curare have been reported by Schmidt and his associates.[139]

Oral administration of myanesin, if effective, is to be preferred, since the effects of intravenous injections are extremely evanescent unless many repeated injections or continuous infusions are used. Berger and Schwartz[169] and others[177–182] working specifically with tetanus have not observed any untoward reactions from large and frequently repeated oral doses of myanesin. The intravenous route is not without some danger of hemolysis. A fatal case of lower nephron-sclerosis has been observed in a patient with severe tetanus who was treated with almost continuous intravenous myanesin (2 per cent), although Schlesinger, Drew, and Wood[166] did not observe any untoward reactions from less continued use.

Myanesin should be added to the physician's armamentarium for the management of tetanus. The drug appears to be effective orally and is not as difficult to manage as curare may be. There is at present no evidence to suggest that deleterious side effects or toxic reactions occur at therapeutic levels. Like curare, myanesin permits control of tetanic spasm without the undesirable narcosis that results from massive sedation. Few physicians will argue that a cooperative patient is not an easier medical and nursing problem than a narcotized one. Florey and co-workers[33] have succinctly pointed up the therapeutic choice – prolonged anesthesia or muscle relaxation by means of curare. At the present writing, myanesin and curare are both capable of accomplishing the desired result of effective muscle relaxation without the dangers inherent in oversedation.

TRACHEOTOMY

The neutralization of circulating toxin and reduction of tetanic spasm are but two of the problems in the management of clinical tetanus. Another objective is the maintenance of an adequate airway and control of secretions. Dietrich[72] agreed that the management of secretions is a difficult problem in tetanus, but could not "accept the dictum – that all cases but the mildest should have early tracheotomy." The decision whether to

perform a tracheotomy on a tetanus patient should rest on the particular circumstances of the case. In a severe case of clinical tetanus with intercurrent pulmonary infections, especially if skilled nursing care is unavailable, tracheotomy should be done. The value of early elective tracheotomy in milder cases lies in the technical advantage of elective versus emergency surgery – in the prevention of obstruction and aspiration rather than the urgent need for treatment of actual obstruction, aspiration, and their complications. Turner and co-workers[187] stressed the respiratory problems of tetanus and added weight to the growing opinion that tracheotomy can be a life-saving measure. Graham and Scott,[188] in discussing the respiratory problems in tetanus, noted the problem of respiratory depression in oversedation, as well as the effect of chest rigidity, shallow respirations, and deficient airway on the development of atelectasis.

Despite the fact that Curling[23] suggested tracheotomy for tetanus in 1837 and Humphrey[189] reported its use in 1856, the procedure has been long in achieving even moderate acceptance in recent years. Harris and co-workers,[190] and Herzon and colleagues[191] have emphasized the great value of tracheotomy in the management of severe and moderately severe tetanus, stressing the factor of respiratory failure as a cause of death. Pathologic studies by Baker[24] and physiologic considerations of Firor[55] and Graham and Scott[188] have reinforced the argument for more frequent consideration of tracheotomy in these cases. Tracheal intubation usually causes entirely too much stimulation. Either or both procedures should be available if curare, especially the intravenous form, is to be used.

SEDATION

No discussion of the management of tetanus can overlook the use of sedation. There can be no disagreement concerning the value of the entire barbiturate group, chloral hydrate, paraldehyde, tribromethanol, ether, chloroform, or any other sedative or anesthetic. However, the clinical disadvantages of prolonged narcosis and anesthesia cannot be dismissed lightly, nor can the report of Firor and associates[192] that barbiturates and tribromethanol shortened the life of animals with tetanus. Curare and myanesin are pharmacologic agents which may be used alone or together and decrease the need for anything but mild sedation. Further, curare and myanesin can be used in combination with the sedative and anesthetic agents and materially decrease the dose requirements of the latter. Various combinations of therapy are possible. MacDonald[186] reported a severe case treated with a combination of myanesin and sodium Pentothal. There appears to be no contradiction to using any combination of intravenous curare, intravenous myanesin, depot curare, or oral myanesin with various sedatives. Sedation, not oversedation, has a definite place in the clinical management of tetanus and is best used in judicious combination with the muscle relaxant drugs. Reliance on sedation alone fails to take advantage of more modern pharmacologic knowledge. In a disease as difficult to manage as tetanus every applicable therapeutic agent should be brought into action.

CHEMOTHERAPY AND ANTIBIOTIC THERAPY

The place of chemotherapy and antibiotic therapy in the treatment of tetanus deserves some discussion. Early in the era of sulfonamides and antibiotics there was considerable optimism regarding the value of these new therapeutic agents.[193] Buxton and co-workers[194] were impressed with the value of penicillin. However, the larger experience of Altemeir[195] "failed to show evidence of any

beneficial effect of penicillin on the course of the disease." Later Diaz-Rivera and associates,[196] on the basis of experience with a still larger group of patients, recommended penicillin for its value in preventing secondary infections and also for its inhibitory effect on the growth of *Clostridium tetani*. Further in vivo studies by Diaz-Rivera, Ramirez, Pons, and Torregiora[197] supported the value of penicillin in eliminating growth and multiplication of the organism and thus preventing "production, diffusion, and fixation of tetanus toxin."

Other antibiotics and the sulfonamide drugs have failed to give any encouraging results. Not surprisingly, cortisone has been administered to at least one tetanus patient with "definite improvement" in the patient.[198] In this case the nonspecific result of mobilizing the resistance forces of the body economy against stress probably was the basis of the beneficial effect. A somewhat different application of cortisone therapy was that reported by Scheinberg,[199] in which an anaphylactic reaction appearing during tetanus antitoxin serum desensitization was successfully managed with cortisone.

DISCUSSION

An inclusive review of the literature dealing with tetanus is virtually impossible. Considering the many erroneous concepts and purely empiric remedies that have been urged in the past, such an inclusive analysis of the subject would create more confusion than clarity. However, on the basis of the material presented, certain broad rules for our guidance may be established.[6]

Recent military experiences with tetanus indicate that modern toxoid prophylactic measures, if utilized to the fullest extent, are capable of reducing the incidence of human clinical tetanus to the vanishing point. Prevention, rather than the necessity for treatment, should be the physician's aim. It is apparent, however, that the best preventive measures are not fully utilized and as a consequence treatment continues to be a clinical problem.

Effective treatment depends upon an understanding of the causative agent and the pathophysiology of the disease. According to Meleney,[200] ". . . It will be seen that the rational treatment of tetanus depends on an accurate knowledge of the pathogenesis of the disease. This is not yet entirely clear, in spite of the clinical and experimental investigations carried on over a long period of time." The characteristics of the responsible organism have been thoroughly studied and identified. However, some characteristics of the organism and its exotoxins need to be studied more completely. The relation of tetanolysin and tetanospasmin to chronic muscle spasm and the reported histologic changes in the muscle is not entirely clear, nor is the exact physicochemcial mechanism known by which the toxin affects the nerve cell.

Despite continuing disagreement, the weight of experimental and clinical evidence indicates that tetanus toxin is disseminated by way of the vascular system alone. Such a concept is in accord with most of the experimental and clinical observations reported.

From a histopathologic viewpoint there exists no evidence that recovery from tetanus is not complete. No convincing permanent structural changes are reported in the nervous system. Many workers during the past century have stressed this fact and have expressed their opinion in a variety of ways that tetanus is a self limited disease. The corollary, often overlooked but frequently stressed in the literature, is that adequate control of the symptoms will result in complete recovery.

Considerable confusion exists as to the relative prophylactic and therapeutic value of tetanus toxoid and tetanus antitoxin. There can be no doubt that circu-

lating toxin can be neutralized by tetanus antitoxin, but there is much doubt that this same toxin can be affected by antitoxin once it has become fixed to nervous tissue and gives rise to clinical symptoms of the disease. Tetanus antitoxin should be used to inactivate circulating free toxin but cannot be considered of any value in controlling the symptoms resulting from toxin already fixed to nervous tissue.

Administration of massive intraspinal and intravenous doses of antitoxin is not only dangerous but also without any firm clinical basis. Intramuscular antitoxin has a definite place in the treatment of symptomatic tetanus by virtue of its ability to neutralize any free toxin which may exist, and it is certainly less harmful than either intraspinal or intravenous administration. Once symptoms of tetanus have occurred, antitoxin is not of primary value in controlling the clinical course of the patient. Other therapeutic measures must be brought to bear.

Control of the symptoms of tetanus can be attempted in two ways. Sedation to the point of narcosis or anesthesia can, unquestionably, prevent tetanic spasm. However, muscle relaxation without profound alteration of the state of consciousness has many advantages. Curare and myanesin are both capable of this. Severe tetanus is already complicated by dangerous respiratory problems and the degree of sedation required to control tetanic muscle irritability almost always aggravates these respiratory difficulties. Curare and myanesin in therapeutic dosages do not result in profound lowering of consciousness and thus have a distinct advantage.

Curare, particularly the aqueous form, can result in respiratory paralysis, but need not do so. Both experimental and clinical observations indicate that subparalytic doses of curare are effective in controlling tetanic muscle irritability and spasm. This subparalytic curare effect is best achieved with the depot (d-tubocurarine in oil and wax) form of administration.

Myanesin, the second muscle relaxant, has a somewhat different mode of action than curare, but is also dramatically effective in controlling tetanic symptoms. The intravenous use of this drug has disadvantages for prolonged use, but oral administration is valuable in the management of tetanus.

Combinations of curare and myanesin will materially reduce the amount of sedation or anesthesia required to control tetanus, thus permitting unaltered consciousness with a resultant gain in ease of patient management in matters of respiratory function, fluid requirements, and general nursing care.

In all but the mildest clinical cases maintenance of an adequate airway and satisfactory control of tracheobronchial secretions may require tracheotomy. Early consideration of elective rather than mandatory emergency tracheotomy may prevent secondary complications such as atelectasis and pulmonary infection.

Antibiotic therapy probably has no specific value in tetanus, but by controlling symbiotic organisms, tetanus toxin production may be decreased. In addition the respiratory problems in severe tetanus make antibiotics valuable adjuncts in treatment.

Surgical care of the wound in traumatic tetanus should be conservative and limited to the usual surgical management of any wound.

Recovery from tetanus is complete and has occurred with all forms of therapy and, indeed, without treatment. This fact, together with the lack of permanent pathologic changes, suggests that if the patient can be kept alive by the measures outlined above, toxin fixed to the nervous system is eventually destroyed and recovery results. Therefore, all properly treated cases of tetanus should recover.

SUMMARY

Since earliest historical times, human clinical tetanus and its management has been an important object of medical investigation. Current morbidity and mortality rates, together with the frequent reports in the literature, attest to the fact that human tetanus is still a medical problem, despite almost perfect methods of prevention.

Gradually increasing knowledge concerning its etiology, pathogenesis, and treatment has been outlined. The history of curare in the treatment of tetanus has been seen to parallel closely the development of modern pharmacologic and neurophysiologic concepts. Despite the fact that the management of tetanus with curare is not new, its rationale has been reemphasized and its value stressed. A newer pharmacologic agent, myanesin, has been discussed in terms of its use in the management of tetanus. The value of tracheotomy has been described.

An outline of the general principles of the management of human clinical tetanus has been offered in the hope that the concepts stressed will be of guidance in establishing the details of treatment in any given case.

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CLINICAL PATHOLOGIC CONFERENCE

Raymond D. Adams, M.D.
Section Editor

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CASE REPORT

History. The patient, a 28 year old white man, was admitted to Birmingham Veterans Administration Hospital on March 23, 1950. He had been in good health until February 1, 1950, when he developed a severe chest cold with cough and pain in the chest lasting several days. The pain then settled in the abdomen, lumbar area, and in the neck and back of the head. On March 1, 1950, he was admitted to a Pomona hospital for two days where a blood Wassermann test was reported negative, but the spinal Wassermann was reported positive. As a result, he was treated with five million units of penicillin. There had been no previous history of a penile lesion or of positive blood test for syphilis. During treatment the patient developed weakness of the legs and had difficulty walking. He also experienced counter-clockwise vertigo. On March 7, 1950, he was admitted to the Los Angeles County General Hospital because of inability to swallow. The mouth was pulled to the right, the left eyelid would not stay open, and vision in the left eye had failed rapidly. A spinal tap was negative for syphilis and for acute poliomyelitis. During 16 days at the county hospital his condition became progressively worse, and four days before transfer to Birmingham V.A. Hospital the patient's left testicle became tender and swollen. At the same time he developed numbness of the fingers and toes.

Past history. The patient had mumps bilaterally at the age of ten. Since the age of 15 he had noted several soft lumps under the skin of the arms and legs. Several of these, diagnosed as "fatty tumors," were removed while he was in the Navy.

Physical examination. On admission to Birmingham Veterans Administration Hospital, the patient was acutely ill with a temperature of 99° F. He showed evidence of marked weight loss, dysarthria, and lethargy, but he was mentally oriented and cooperative. The pharynx was slightly red. The lungs were clear to percussion and auscultation; no rales were heard. The breath sounds were normal. The heart was of normal size; the rate was 120 and regular. Examination of the abdomen revealed no tenderness or abnormal masses, and the liver and spleen were not palpable. The left testicle and epididymis was extremely tender and swollen. There was mild tenderness over the seventh thoracic spinous process and in the iliosacral regions bilaterally. All extremities were markedly emaciated, particularly the legs. There was pes cavus of the right foot. There was a diffuse, macular, erythematous rash about the neck and chest. There was mild enlargement and tenderness of the inguinal lymph nodes bilaterally.

Neurologic examination (cranial nerves). The sense of smell was normal. Vision was grossly normal. The visual fields were full to gross testing. The fundi showed blurring of the disks bilaterally without measurable elevation. The retinal veins were full. Bi-

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lateral droop of the lids was a result of paresis of the levator palpebrae muscles. There was paralysis of lateral gaze with the right eye and paresis of lateral gaze in the left eye. Weakness and subjective double vision were noted on looking down and center with both eyes. The corneal reflexes were absent bilaterally. Hypesthesia was found in the second and third divisions of the trigeminal nerve with paresis of the muscles of mastication bilaterally. A complete bilateral peripheral facial paralysis was present. The hearing was normal bilaterally. The palate was weak on elevation. The patient had dysphagia and dysphonia. The tongue could not be protruded normally.

Sensory examination. Bilateral hypalgesia without hypesthesia was present from C-2 through C-7. Pain, touch, vibration, and position senses were normal in the lower extremities.

Reflexes. The biceps and triceps reflexes were hypoactive and equal. The superficial abdominal reflexes were present. The knee and ankle jerks were 1 plus. There were no pathologic toe or finger signs. The Kernig and Brudzinski signs were positive.

Cerebellar tests. Bilateral ataxia and dysmetria in finger to nose tests were demonstrated.

Laboratory studies. The red blood count on admission was 4,250,000, hemoglobin 11.8 gm., and the white blood count 8,700, with polymorphonuclear leukocytes 61 per cent, lymphocytes 36 per cent, monocytes 3 per cent, eosinophiles 0, basophiles 0, and blast forms 0. Spinal fluid examination showed 182 lymphocytes with 116 mg. of protein. The fluid was clear, the pressure and dynamics normal. A portable chest x-ray at 60 inches distance showed no abnormalities.

Course in hospital. Twenty-four hours after admission, the patient began to run a fever which lasted 72 hours with the temperature up to 104° F. on two occasions. He was placed on Aureomycin, Chloromycetin, and Crystacyllin and there was a drop in temperature. The patient was seen on March 25, 1950 by Dr. J. M. Nielsen, senior consultant in neurology, who made a diagnosis of meningoencephalomyelitis of viral origin. The patient continued to improve slowly but began to have periods of disorientation and confusion. His appetite remained poor and his strength very weak. On April 1, the only cranial nerve involvement noted was residual weakness of the third and seventh cranial nerves bilaterally. At this time the patient developed an epididymitis which apparently responded to medication, but the swelling in the epididymis and testicle never disappeared. All antibiotics were stopped at this time. The patient required more or less continuous sedation because of severe low back pain. The daily fluid intake was around 6,000 cc. and the output 5,000 cc. This was explained by presumed involvement of the hypothalamus. On April 14 the patient's hemoglobin dropped to 9 gm. and the persistent anemia became more severe. The patient received 1,000 cc. of whole blood. He remained confused although he was able to be in a wheelchair for part of the day. The patient developed exposure keratitis from incomplete lid closure due to his bilateral seventh nerve weakness.

On April 12 the blood count showed 3,250,000 red blood cells, hemoglobin 10.2 gm. and 7,900 white blood cells. At this time he had an abnormal differential showing 46 per cent polymorphonuclear leukocytes, 30 per cent lymphocytes, and 22 per cent monocytes, with 2 basophils.

On April 17, 1950 temperature was 98° F., pulse 88, respirations 20. The patient was able to swallow better and was placed on a soft diet. On April 25 he was again seen by Dr. Nielsen, who found marked weakness with generalized muscular atrophy including the face. The sense of smell and visual fields were normal. Papilledema was present and there was a bilateral sixth nerve weakness. The left pupil was dilated and reacted sluggishly to light. There was recovery of sensation in the face but the patient had trouble hearing with the left ear. The face was completely paralyzed bilaterally with a Bell's phenomenon. All deep reflexes were absent and a Babinski sign was found on the left. The superficial abdominal reflexes were present.

On May 6 temperature was 103° F., pulse 120, respiration 14. At this time disassociated movements of the eyes developed and the patient was placed in an oxygen tent. A Levine tube was introduced into the stomach because of abdominal distention. On the same evening the temperature was 103° F., pulse 140 and respirations 15. Blood pressure was 120/80. Papilledema was present with retinal hemorrhages. For the first time the spleen was palpable at the left costal margin, and the liver two fingerbreadths below the right costal margin. Large inguinal lymph nodes were present bilaterally. Because of the lack of im-

provement, a blood count was ordered which disclosed the following unexpected findings: the total white count was 240,000, and a smear disclosed numerous young cells, probably immature myelocytes. The fluid aspirated from the Levine tube showed evidence of recent bleeding. The stool showed the presence of occult blood. The patient began to bleed rapidly following attempted venepunctures, and large areas of ecchymosis developed. The red blood count was 3.7 million and the hemoglobin 10 gm. Hematocrit study showed one-fifth of the cells to be white blood cells. At this time a diagnosis of myelogenous leukemia was made and the patient was given blood transfusions.

On May 6 the total white count was 278,000. The patient was markedly weak, perspiring profusely, and the platelet count was 20,000. A course of aminopterin and toluidine blue was given. Within 24 hours the patient developed visual hallucinations and became terminal, dying that evening.

The laboratory data obtained during the patient's illness are summarized in table 1.

DISCUSSION

DR. C. W. OLSEN (senior consultant in neurology): The history on admissions was that of the invasive stage of an infectious illness, followed by polyneuritis, meningitis, and encephalomyelitis. The possibility of syphilis was fairly well excluded. A history of mumps at age ten made epidemic parotitis unlikely, in spite of epididymoorchitis. However, the testicular infection might well be due to retention of urine.

The blood count on March 8 showed stimulation of leukocytic elements, with a fairly even distribution except for some relative increase in monocytes. The spinal fluid on that date showed evidence of meningeal irritation and increased intracranial pressure. The finding of subcutaneous nodules brought in a suspicion of neurofibromatosis.

Enlargement of inguinal lymph nodes in the absence of tributary infection should arouse suspicion of general lymphoid stimulation. (The lymphatic drainage of the testes is toward pelvic rather than inguinal nodes.)

The neurologic findings are more suggestive of a diffuse or disseminated reaction rather than any single focus of dis-

TABLE 1
SUMMARY OF LABORATORY DATA

Date	*RBC*	*Hgb.*	*WBC*	*PMN*	*Lymphs*	*Mono.*	*Eos.*	*Baso.*	*Blasts.*
3/24/50	4.25	11.8	8,700	63	36	3	0	0	0
3/24/50	Spinal Fluid – 182 lymphocytes, 116 mg. protein, normal pressure, clear fluid								
3/27/50	4.92	14.5	8,750	54	35	4	6	1	0
3/28/50	Spinal Fluid – 28 lymphocytes, 130 mg. protein, clear fluid, normal dynamics								
4/4/50	4.08	12.1	9,050	52	39	7	1	1	0
4/12/50	3.25	10.0	7,900	46	30	22	0	2	0
4/18/50	4.19	13.2	–	–	–	–	–	–	–
4/26/50	3.82	12.1	–	–	–	–	–	–	–
5/5/50	3.70	10.2	278,400	16	64	11	10	–	8
				5 stabs, 1 juv., 1 promyelocyte, many unclassified basket cells					
5/5/50	NPN 41 mg. per cent CO_2 50 vol. per cent (equiv. to 22.4 mEq/L).								
5/6/50	3.35	10.5	210,000	14	78	8	1 promyelocyte, 22,000 platelets		
5/7/50	3.59	10	142,000	10	87	0	1	2	–
				3 promyelocytes, 1 blast.					

ease. Recheck of the spinal fluid on March 24 and 28 showed an increase in the cell count with persistence of increased protein. A remarkable change in the leukocyte count is suggested by comparison of the March reports with those in May, and the predominant increase in lymphocytes is consistent with lymphoid leukemia, especially considering the splenomegaly and increasing lymphadenopathy. Meanwhile the evidences of involvement of the central nervous system altered a little and hallucinations were reported. Several agglutinations for specific viruses were negative. Antibiotics were administered but without evident benefit.

In retrospect, this case is one of lymphoid leukemia with early neurologic symptoms. Infectious mononucleosis must be considered in differential diagnosis.

In neurologic practice, as contrasted with general practice, leukemia commonly has neurologic complications. The interesting thing in this case is that the nervous symptoms cannot be fully explained by such characteristic lesions of leukemia as leukocytosis, cellular infiltration, thrombosis, and hemorrhage. This raises the question of the presence of a neurotoxin or neurotropic virus associated with some leukemias, that is, an agent noxious to the nervous system as well as to the hemopoietic system. The neurologic complications of infectious mononucleosis represent such a relationship.

NECROPSY REPORT

DR. B. E. KONWALER: The body was that of a somewhat cachectic but otherwise normally developed white male who appeared to be about 30 years of age. The important findings on external examination were: first, the presence of a few cervical lymph nodes which were palpable externally; second, the presence of a number of petechiae, especially over the extremities and over the anterior chest; and third, the definitely enlarged liver and spleen which were readily palpable below the costal margins. On opening the thorax a large greyish-white, firm mass was seen in the anterior mediastinum. The mass measured approximately 7x5x4 cm. and partially encircled the trachea, but did not significantly narrow the lumen of the trachea. The mass extended superiorly to surround some of the major vessels at the base of the neck, but here again the lumens of vessels were not significantly narrowed. The parietal pleura in both pleural spaces contained a few nodules, greyish-white to light pink in appearance and of rather firm consistency. On cut section these nodules had approximately the same color as the mass just described in the mediastinum.

The heart was not enlarged, weighing only 250 gm. In the midportion of the interventricular septum, mainly in the anterior half, there was seen a 1 cm. greyish-white nodule. This nodule was quite firm and again had the appearance of the tumor nodules described previously. The endocardium had a smooth, glistening, white appearance. The valve measurements were all within normal limits and there was no significant atherosclerosis of the coronary vessels.

Both lungs were somewhat wet and boggy, the right weighing 700 gm. and the left 750 gm. On pressure of the lungs, fluid exuded readily from the cut surfaces. The liver was considerably enlarged, weighing 2,700 gm. The cut surface had a deep brown color and scattered throughout were a number of small, greyish-white nodules. The bile ducts including the hepatic and common bile ducts were markedly dilated and filled with thin, green bile. Tumor tissue extended into and surrounded the common bile duct narrowing the duct and in one area apparently completely obstructed the lumen. The gallbladder wall was similarly involved and several

large plaques of greyish-white tumor tissue were seen in the thickened wall. The lumen of the gallbladder was filled with thin, green bile.

The pancreas was surrounded by a mass of lymph nodes which was firmly attached to it; it was not possible to differentiate pancreatic tissue from lymphoid tissue readily on gross examination. The entire pancreas appeared to be replaced by greyish-white tumor tissue. Very little normal coloring or pattern to suggest pancreatic tissue was seen.

The spleen weighed 1,500 gm. Here again, the cut surface did not resemble spleen at all but had a homogeneous paste-like appearance with numerous areas of softening.

The gastrointestinal tract showed grossly no definite plaques of tumor tissue within the wall, although the wall was somewhat firmer than usual.

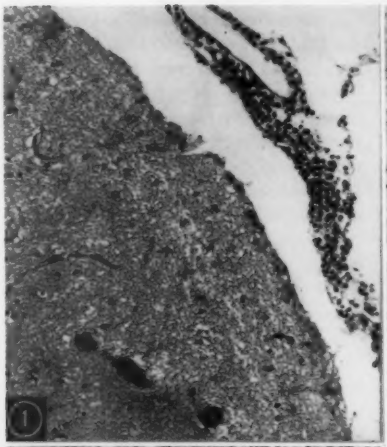
The kidneys together weighed 350 gm. and the cut surfaces showed numerous nodules of greyish-white tumor tissue in the cortex and some in the medulla. The nodules varied in size from 1 to 2 cm. The left ureter was surrounded and partially compressed by nodules of tumor tissue, but there was no apparent interference with urinary flow in this ureter since the ureter was not dilated above the site of compression.

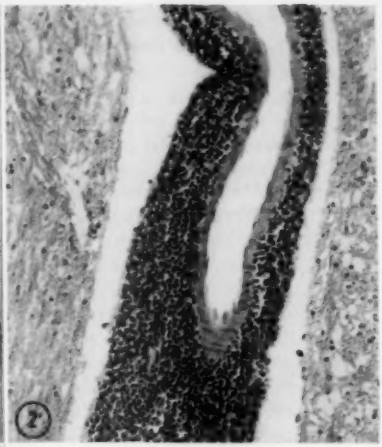
The lymph nodes over the entire body were markedly enlarged. Large masses of lymph nodes were found in the mesentery and retroperitoneal areas. On cut section the lymph nodes all showed a greyish-white appearance resembling the tumor tissue described elsewhere.

Bone marrow samples removed from the sternum, the vertebra, and from the upper portion of the right femur all showed apparent cellular infiltrations and had a greyish-red appearance.

Microscopically all of the tumor tissue showed a very similar cellular pattern. Neoplastic cells consisted of undifferentiated leukemic cells measuring from 15 to 20 micra in diameter and having a very scant rim of cytoplasm, or in some cells no cytoplasm at all. The nuclei had definite nuclear membranes and the nuclear chromatin tended to form small knots. Most of the nuclei were fairly round in shape, although occasionally a lobulated nucleus was seen. The infiltrates in the kidney, pancreas, spleen, liver, heart, and bone marrow were very extensive. In the kidney most of the cortex was replaced by leukemic infiltrate and the glomeruli and tubules were, for the most part, destroyed. Similarly, in the pancreas most of the pancreatic tissue was destroyed by the extensive leukemic infiltration. The same was true for most of the other organs. Although grossly no definite infiltrates had been noted in the gastrointestinal tract, on microscopic section every section studied showed infiltration by leukemia cells. Similarly, the genitourinary system showed leukemic infiltrates in all sections studied, including testicles and prostate. Sections of the bone marrow from the sternum, spine, and femur all showed replacement of the normal bone marrow by solid sheets of leukemic cells. It was felt that this should be classified as a stem-cell leukemia with very extensive visceral infiltration.

DR. J. S. BERRYMAN: Examination of the brain after fixation in formalin showed generalized congestion of all superficial vessels, with a small angiomatous malformation in the left cerebellopontine angle. There was moderate opticochiasmatic arachnoiditis. There were no gross areas of softening. The cranial nerves at the base of the brain were present and intact. The blood vessels at the base of the brain were normal. Sections through the brain showed generalized cerebral edema, with narrowing of the sulci and broadening of the gyri. There was evidence of congestion throughout the white and grey matter. Congestion was also noted in the basal ganglia and thalamus.





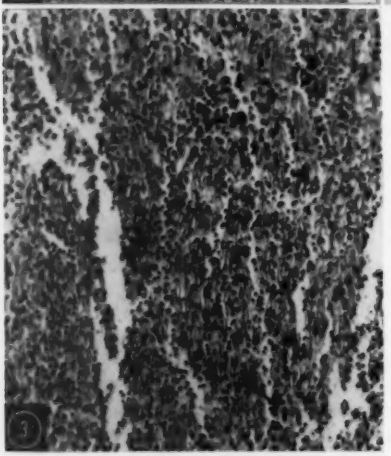


FIG. 1. Frontal cortex and leptomeninges showing leukemic infiltration of pia and perivascular spaces.

FIG. 2. Leukemic infiltration about a small artery.

FIG. 3. Oculomotor nerve showing extensive invasion and fragmentation by leukemia cells. Hematoxylin and eosin stains.

The third ventricle was slightly dilated. The substantia nigra and red nucleus could be identified grossly and the only lesion noted was congestion. Sections through the level of the third nerve nucleus showed no gross lesions. The brain stem was rather soft due to poor fixation. There was a definite tonsillar herniation bilaterally but no evidence of pressure exerted on the medulla. Serial sections from the brain stem down to the spinal cord disclosed only intense congestion in the grey matter and to a lesser degree of the white matter. No gross areas of softening could be identified.

Microscopic: Hematoxylin and eosin stained sections of the occipital and frontal cortex disclosed round cell tumor infiltration in the leptomeninges and in the perivascular spaces of the cortex and white matter (figure 1). There were up to five layers of cells surrounding some of these vessels, particularly in the white matter. The vertebral artery showed

heavy infiltration of the adventitia (figure 2). There was no direct invasion of the cortex or white matter. These cells making up the exudate in the perivascular spaces were round, small, dark-staining cells consisting almost entirely of nucleus with little or no cytoplasm. They appeared to be immature white blood cells. There was some early organization by fibroblasts. Mitotic figures were evident. The architecture of the cortex and individual neurons was normal.

A section through the midbrain at the level of the red nucleus and substantia nigra showed the lining of the aqueduct to be normal. There was marked thickening of the leptomeninges in the interpeduncular fossa with extensive infiltration of the third nerve fibers by tumor cells (figure 3). This infiltrate continued into the substance of the brain stem on the medial aspect of the cerebral peduncles in the form of a perivascular extension. The neurons of the substantia nigra, red nucleus, and reticular formation of the brain stem were normal. The mesencephalic tegmental nuclei showed some decrease in the number of neurons and evidence of atrophy with shrinkage. A section through the mid-pons showed very little infiltration of the leptomeninges. All perivascular spaces in the basilar and tegmental portion of the pons showed collections of tumor cells. The pontine tegmental nuclei appeared normal. The neurons of the sixth cranial nerve nucleus showed altered staining reactions with pyknotic nucleoli and edema of the neurons. There were occasional nerve cells showing sclerosis. Tigrolysis was evident. Sections through the fifth cranial nerve nuclei showed poor staining of the neurons and tigrolysis. Many of the large neurons of the reticular formation showed poor staining with dissolution of their nuclei. Sections through the middle of the medulla at the level of the inferior olivary nucleus showed the previously mentioned extension into the leptomeninges, and infiltration of the eighth and ninth cranial nerves. There were numerous perivascular hemorrhages in the medullary tegmentum. The tegmental nuclei were well preserved except for altered staining reactions. All blood vessels were congested. The seventh nerve nucleus was identified, and the neurons showed nothing more than central chromatolysis. Sections through the lower medulla including the twelfth nerve nucleus showed evidence of central tigrolysis of the neurons. Sections through the upper cervical spinal cord showed normal anterior horn cells, and collections of tumor cells in the leptomeninges.

NEUROPATHOLOGIC DIAGNOSIS: Leukemic infiltration of the perivascular spaces and cranial nerves of the brain, with secondary central chromatolysis of the corresponding neurons.

SUMMARY AND CLINICAL CORRELATION

This is a case of a 28 year old white man who presented himself with symptoms chiefly indicative of involvement of the nervous system. On March 14, 1950, a blood count had revealed 20,000 white blood cells with a differential in which 13 monocytes and 34 lymphocytes were seen in 100 counted cells. At that time the patient also had a hemoglobin of 12.5 gm. In view of this rather indefinite blood picture, the possibility of a blood dyscrasia was not considered. Terminally, however, the patient definitely developed a leukemic blood picture with white counts running as high as 240,000 and classical sternal marrow studies indicative of an acute leukemia, undifferentiated, and of a stem-cell type. At necropsy the patient showed very extensive visceral involvement of every organ in the body with the exception of the thyroid and adrenal glands.

CASE REPORT

BAL Therapy of Acute Porphyrinuria

Henry A. Peters, M.D.

THE medical literature is replete with treatises on acute intermittent porphyria. To date therapy has been unrewarding.

A case of acute porphyria with severe neurologic manifestations including a recurrent and toxic schizophrenic-like psychosis, bulbar cranial nerve dysfunction, motor neuropathy, and hypertension failed to respond to phenobarbital withdrawal, supportive measures, and ACTH therapy. Dramatic improvement followed the institution of BAL (2,3-dimercaptopropanol) when death seemed imminent.

Mortality during the acute episodes of intermittent or acute porphyria, especially with severe neurologic manifestations, is given as high as 80 or 90 per cent.[1] Frequent causes of death are respiratory failure resulting from bulbar involvement, secondary infections, particularly pneumonia, and hepatic insufficiency. Intensive therapy with vitamins and ACTH has been disappointing.

According to Nesbitt,[2] there is no specific or satisfactory therapy for acute porphyria and only symptomatic or supportive measures are available. Intravenous procaine was reported by Mellinger and Pearson[3] to have affected a case of acute porphyria favorably, and Grubschmidt[4] reported a case with neurologic complications that seemed to respond to procaine. Since the patient reported here did not have severe pain during her critical course, intravenous procaine was not utilized until later during convalescence to control the pain which occurred then. ACTH has been tried unsuccessfully by investigators,[3,5] with suggested improvement in single cases,[6,7] but only when features of Cushing's syndrome were produced using 680 units in six days.[7] Abnormal porphyrins persisted in the urine despite this therapy in both cases.[6,7] In the present case, ACTH was administered by intravenous drip, 25 mg. over eight hours, but until the addition of BAL and B_{12} the course appeared fulminating with marked aggravation of the psychosis.

Because of the impression that BAL alone was responsible for improvement, this paper is submitted to stimulate clinical trial by others since the rarity of the condition (or the absence of recognition) makes a series of cases improbable.

CASE REPORT

A 52 year old woman was admitted to University Hospitals on December 12, 1953, in a disoriented, hallucinatory state. Four years earlier she had been bedridden for two weeks with weakness in her legs. Red urine which she had observed at that time was disregarded because she thought it was due to a red medicine she was taking.

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The current illness began November 8, 1953, with abdominal pain, followed by weakness in the legs, urinary incontinence, and later mental confusion. Phenobarbital had been taken daily for four years for "nervousness." In addition to the toxic type of psychosis on admission to the hospital, there was generalized muscular weakness with hypoactive reflexes. Temperature was 100°, pulse 88, respirations 32, and blood pressure 168/108. Her urine stained the bed sheets pale red. The electroencephalogram showed moderate diffuse abnormality with low to moderate voltage 8–10/second waves and low voltage fast activity in all leads. Bromide, lead, and arsenic values of the blood and urine were normal. Before the diagnosis of porphyria had been established, a regitine test for pheochromocytoma showed a prompt fall from 170/120 to 100/70. This was repeated the following day with similar results. Psychosis cleared the second day of hospitalization.

The first examination for urinary porphyrins was made December 13, with the finding of 5+ coproporphyrin and 3+ uroporphyrin, and daily determinations thereafter were strongly positive including porphobilinogens.

Therapy was initiated in the form of ACTH, crude liver, and general supportive measures. This failed to alter the abnormal porphyrin excretion; 36 hours later a recurrence of psychosis ensued along with more alarming signs of motor paralysis, dysphagia, blurred vision, tremors, and alternating hypertension and hypotension. ACTH was stopped on the third day.

On December 23 the patient became comatose, with Cheyne-Stokes respirations. One dose of ACTH was again given, plus 1,000 micrograms of B_{12} intramuscularly. As a final effort 0.5 cc. of BAL was administered; a second dose was given two and a half hours later. An hour after the second injection of BAL she recovered consciousness, and was lucid and coherent. Thereafter she was given BAL, 0.5 cc. of 10 per cent solution, three times daily for 12 days. The abnormal porphyrins disappeared from the urine and her clinical condition improved. BAL was stopped January 1, 1954, by which time she had received 180 mg. of the drug. Uroporphyrin reappeared in the urine and persisted until injections of BAL were resumed January 11. During the subsequent four days, 80 mg. more was administered. BAL was stopped permanently on January 15. Porphobilinogen was slightly positive in the urine the next day but absent the second day and thereafter. Uroporphyrins reappeared in slight amount in several isolated 24 hour samples over the next three weeks, but did not persist. BAL added to the urine samples containing uroporphyrin did not alter the fluorescence in vitro.

The clinical course had been one of daily improvement in strength, return of bladder continence, and stabilization of vital signs. Pain in the extremities occurred in the last two weeks and was treated initially with several injections of intravenous procaine, but small doses of cobra venom have since proved adequate. The patient was discharged on February 20, 1954. Follow-up report on March 13, 1954 indicated that the patient was walking with slight assistance and continued to show daily improvement. No pain remains and abnormal porphyrins have not recurred in the urine. Since discharge she has been receiving a weekly injection of BAL.

DISCUSSION

Acute intermittent porphyria is the most common form of porphyria. It is transmitted hereditarily as a Mendelian dominant gene and occurs in women three times more often than in men. The possibility of porphyria should be entertained in any case with unusual abdominal complaints and symptoms referable to the central nervous system, such as toxic or schizophrenic-like psychosis, peripheral neuropathy, or an ascending Landry's type paralysis.[8] The clinical picture is bizarre and often resembles hysteria, according to Waldenström[9] who points out that symptoms may not always be accompanied simultaneously with abnormal porphyrin excretion.

The attacks have occurred after prolonged ingestion or contact with lead, acetanilid, nitrobenzol, Sulfonal, Trional, sulfanilamide, and barbiturates, but whether these are the causative or aggravating agents is not known.[10] The patient reported here had used barbiturates for four years to control hypertension and neurotic manifestations that conceivably arose from porphyria.

Why BAL was effective in this case is a matter of conjecture. Other neurologic conditions such as Wilson's disease have responded to BAL and the copper ion has been implicated as the causative agent by Zimdahl, Hyman, and Cook.[11] BAL had been used in severe peripheral neuropathies by Furmanski[12] and by the author with debatable results. For this reason it was tried in this case of acute porphyrinuria with peripheral motor neuropathy. The lithium ion has been shown to produce a reversible, chorea-like disorder.[13] Sumegi and Putnoky[14] observed that lead, mercury, bismuth, copper, zinc, iron, silver, and gold caused white rats to develop weight loss, hyperfunction of the thyroid, and porphyrinuria.

B_{12} in dosage of 1,000 micrograms daily was also initiated during this patient's severe crisis and may have had a favorable influence on metabolism. However, B_{12} alone did not prevent return of uroporphyrin in the urine when BAL was stopped. Hence it is believed that BAL alone was responsible and her consistent improvement following therapy causes one to be optimistic regarding complete recovery.

The abnormal porphyrins are excreted in urine and feces as the zinc metal complex, according to Watson and Schwartz.[15] By their excretion in acute porphyrinuria the zinc porphyrins may rob important cellular enzyme systems, thus bringing about a cellular metabolic deficit sufficient to cause severe damage to the nervous system, especially the peripheral nerves. BAL may act by removal of zinc or another heavy metal which presumably is responsible for this pathologic zinc porphyrinuria, thus halting the removal of essential porphyrins from the body.

SUMMARY

BAL administration seemingly reversed a terminal case of acute intermittent porphyria with severe neurologic complications after adequate ACTH therapy had failed. Administration of BAL was followed by cessation of abnormal porphyrin excretion on two occasions. The possibility of zinc or other heavy metal toxicity as the primary cause of acute porphyria is suggested. Further study of BAL therapy in acute and chronic porphyria is warranted to determine its influence in arresting this metabolic disorder.

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CASE REPORT

Shoulder-Hand Syndrome Following Hemiplegia

Daniel M. Swan, M.D.

THE TERM "shoulder hand syndrome" is one which is used to describe painful disabilities of the upper extremity due to disturbances of the sympathetic nerve supply. The vasomotor and trophic symptoms seen are considered to result from reflex stimulation of the sympathetic nervous system. All disabilities of this type probably have a common or similar underlying neurovascular mechanism. This syndrome is most commonly seen in association with myocardial infarction, trauma, and hemiplegia. It has been observed less frequently after herpes zoster, nodular panniculitis, gonococcal arthritis, diffuse vasculitis, cervical osteoarthritis, thrombophlebitis, and periarteritis nodosa.

It is thought that any external or internal disturbance or violence to tissue may set up the afferent stimuli which activate the internuncial pool in the cord, creating a disturbance affecting the anterior and lateral horn cells which innervate the shoulder and upper extremity. The clinical manifestations of the shoulder hand syndrome, which may last from weeks to years, consist of painful shoulder disability and limitation of motion, associated with swelling, color changes, and pain and stiffness of the hand and fingers. The shoulder manifestations may closely resemble periarthritis. The elbow is rarely involved. Color changes in the hand and fingers may vary from deep erythema to cyanosis or pallor. The temperature of the hand is sometimes elevated, especially in the early stages. Later developments may consist of flexion deformities of the fingers, atrophy of the subcutaneous tissues, trophic changes of the skin, osteoporosis of the bones of the hands, tendon contractures, and subluxations.

Chevallier[1] in 1867 first noted that vasomotor changes may occur in extremities affected by cerebral accidents. Many other reports on patients with hemiplegia have mentioned symptoms and signs similar to those of the reflex dystrophy known as the shoulder hand syndrome. DeTakats[2] and Evans[3] noted that causalgic states may follow cerebral vascular accidents. Steinbrocker and co-workers[4] consider that the vascular lesion which impairs motor function may also interfere with the central autonomic nervous system control, thus predisposing to later development of the syndrome. The symptoms of the reflex dystrophy may range from a mild form to the prolonged, progressive picture described above.

Treatment of the shoulder hand syndrome has variously consisted of ortho-

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NEWSLETTER

JUNE, 1954

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Epilepsy League Meets In Washington The American Branch of the International League Against Epilepsy held its annual meeting at the Shoreham Hotel in Washington (May 1 and 2). Following a joint morning session with the American Academy of Neurology, the scientific sessions began on the afternoon of May 1st and continued until noon the next day. The program was broad in scope, covering aspects of the pathophysiology and diagnosis of seizures; new forms of treatment; and socio-economic factors in epilepsy as revealed by a Gallup Poll survey of public attitudes toward epilepsy (William Caveness) and the question of accident rates among epileptics (Harry Sands) .... The newly elected League president for 1954-1955 is Russell N. DeJong. A. Earl Walker was re-elected vice president, International League, and Jerome K. Merlis, secretary-treasurer. Francis L. McNaughton was added as a new member of the council.

Conference On Nerve Regeneration Held At NINDB Under the auspices of the National Advisory Neurological Diseases and Blindness Council, a conference was held at the Clinical Center of the National Institutes of Health (May 7-8) to review present studies on regeneration in the central nervous system, as well as to formulate plans for future investigations. Under the chairmanship of Louis B. Flexner of the University of Pennsylvania, 16 outstanding neurologic scientists convened at a round table symposium. Among them were key representatives from leading universities in this country, and also from Oxford and Melbourne Universities, the Rockefeller Institute, and the Massachusetts Institute of Technology. Included in the program were discussions on structural regeneration and functional restitution in various animal species from fish to man. The chief discussants of the presentations were Howard Holtzer, Grayson P. McCouch, Ralph W. Gerard, and William F. Windle. It is planned that the proceedings of this conference be published as a monograph.

Directory of Motion Picture Films and Authors C. D. Young, director of Professional Publications, 2010 Kentucky Street, Lawrence, Kansas, announces a forthcoming "Directory of Professional Motion Picture Films and

Authors," to enable officials of state and other societies, university faculty members, program chairmen, hospitals, film authors, educators, and so on, to locate, evaluate, and procure a suitable film with a minimum of time and effort. It is intended that the new directory will serve to prevent duplication of effort by film authors here and abroad, thus enhancing the value of future films. Although information on nearly 4,275 films has been compiled, the number of useful films produced is still unknown, according to Mr. Young. Therefore, he requests all film authors to write immediately for film questionnaires, regardless of the availability of their films. Members of the medical profession are also invited to provide the film title and name and address of any film offer.

* * * * * *

Prize For Manuscript On Neurology President Howard D. Fabing calls attention to the prize of $100, graciously offered by the Woman's Auxiliary, for the junior member of the Academy who submits the most outstanding manuscript on any aspect of neurology, to be submitted to the prize committee before December 1, 1954. A similar prize will be awarded in 1955 and 1956. To qualify, the junior member need not be the sole author of the manuscript, but he must be the major contributor. The prize committee consists of Mrs. James L. Sagebiel of the Woman's Auxiliary, and four members of the Academy Board of Trustees: T. J. C. von Storch, A. R. Vonderahe, L. E. Daniels, and Titus H. Harris. Candidates for the prize should submit their manuscripts to the AAN Executive Secretary, Mrs. J. C. McKinley, 19 Millard Hall, University of Minnesota, Minneapolis 14, Minn.

Dues Increased in Some AAN Membership Categories In order to meet the rising costs of holding meetings and the needs of the expanding Academy program, the president and the board of trustees recommended an increase in dues from $5.00 to $10.00 a year for fellows, active members, and associate members who are in clinical practice. This recommendation from the president and board of trustees was voted affirmatively by the membership in executive session. According to the new schedule, junior and associate members not in clinical practice will not be affected; their dues remain at $2.00 a year .... In the future, also, subscriptions to the journal will be placed on a calendar year basis to conicide with the statement for dues. To make this possible, members will be excused from dues for six months, and in the fall of 1954 they will be sent a statement for dues and subscription to the journal extending to

January 1, 1956. Thereafter, all bills will be sent out, for both Academy dues and the journal, on a calendar year basis (January 1 to December 31).

Current NINDB Training Awards In Neurology During the current year, 17 institutions are receiving grants from the National Institute of Neurological Diseases and Blindness for the graduate training of educators and clinical researchers. The institutions receiving these awards, with their respective program directors are: Jefferson Medical College, (Bernard J. Alpers); University of Louisville, (Ephraim Roseman); University of Cincinnati, (Charles D. Aring); University of Michigan, (Russell N. DeJong); New York University, (S. Bernard Wortis); University of Minnesota, (A. B. Baker); Georgetown University, (Francis M. Forster); State University of Iowa, (A. L. Sahs); Columbia University, (H. Houston Merritt); University of Kansas, (A. T. Steegmann); University of North Carolina, (Thomas W. Farmer); University of Vermont, (George A. Schumacher); University of Chicago, (Richard B. Richter); Albany Medical College, (Robert W. Graves); University of Utah, (Madison H. Thomas); Northwestern University, (Benjamin Boshes); and Washington University, St. Louis, (James L. O'Leary and Henry G. Schwartz).... Applications for training grants in neurology, or inquiries about the program, should be forwarded to Dr. Frederick L. Stone, Chief, Extramural Programs, National Institute of Neurological Diseases and Blindness, Bethesda 14, Maryland.

* * * * * *

New Appointments In Barcelona Announcement is made by Dr. L. Barraquer-Bordas, secretary of the Neurological School of the Hospital de la Sta. Cruz Y S. Pablo, Barcelona, of new appointments to the staff of this famous school. Among those appointed as neurosurgeons are Dr. A. Bachs, pupil of Doctors A. Ley and A. Earl Walker, and F. Duran, pupil of E. Tolosa and J. Paiklas. Dr. J. Vila, who recently worked with Robert Schwab, and Dr. J. M. Samso are in charge of the section of electroencephalography. Dr. J. Canadell, pupil of A. Santos-Palazzi, will have charge of a section on neuro-orthopedic problems. This neurologic school was founded in 1882, and today is directed by Prof. L. Barraquer-Ferre.

Prof. Monrad-Krohn To Visit U. S. A. Under the auspices of the National Multiple Sclerosis Society, Prof. G. H. Monrad-Krohn of Oslo will address the staffs of various neurologic clinics and institutes in the U. S. A. during June and July. Starting at the New York Neurological Institute, he will attend the meeting of the ANA in Atlantic City (June 14-16);

then visit the National Institute of Neurological Diseases and Blindness in Bethesda; next swinging westward through Galveston and Houston, he will visit A. B. Baker in Minneapolis, the Mayo Clinic, University of Wisconsin, and various institutes in Chicago. His tour terminates in New York, July 7.... Prof. Monrad-Krohn, for years the central figure in Norwegian neurology, founded the independent university clinic at Rikshospitalets in Oslo. Author of the classical volume, "Clinical Examination of the Nervous System," he is internationally noted as a teacher, clinical researcher, and medical philosopher. In addition, his plurilinguistic talents, cultivated in a distinct personal charm, have gained him renown as a unique raconteur.

Here and There The German Society for Neurosurgery has elected as honorary members Prof. Dr. R. Wartenberg, San Francisco (Honorarprofessor of the University of Freiburg i. Br.), Prof. Dr. L. Schonbauer, Vienna, and Prof. Dr. P. Bailey, Chicago. Dr. Wartenberg has left for Freiburg i. Br., Germany, where he will be guest professor for half a year. His address is: Nervenklinik, Freiburg, i. Br., Germany, (17b).... The Third International Poliomyelitis Conference will be held in Rome, Italy (Sept. 6-10). Information about the meeting may be obtained from the Secretariate, Third International Poliomyelitis Conference, Via Lucullo 6, Rome, Italy.... The sixteenth annual Walter Niles Memorial Lecture was given by Derek Denny-Brown of Harvard in the Cornell University Medical College, April 16. His topic: "Visual Motor Mechanisms in the Cerebral Cortex." Dr. Niles was professor of medicine and dean of the Medical College before his death in 1941.... The 1954 Conference of the National Rehabilitation Association was held at the Claridge Hotel, Atlantic City (May 13-14). Topic of the conference: "The President's Proposals to Expand Rehabilitation Services".... A new seizure clinic and EEG laboratory has been opened at the St. Joseph Hospital, Phoenix, Ariz., under the direction of John R. Green.... Distinguished visitors to the U. S. A. recently were: Dr. Ruedi Hess, electroencephalographer, Zurich, Switzerland; Dr. Eric Kukelbert, an outstanding authority in electromyography, Neurophysiological Institute, Stockholm, Sweden; and Dr. Jerzy Olszewski, neuroanatomist, Montreal Neurological Institute....

Percy Bailey

pedic and physiotherapeutic measures, radiation, and surgical procedures involving appropriate sections of the sympathetic nervous system. Good results have been reported with stellate ganglion block, regardless of etiology. This paper presents a report of three patients who developed the shoulder hand syndrome following cerebral vascular accidents, and were treated by means of procaine block of the stellate ganglia. The technic employed was the anterior approach described by McGowan,[5] which is suitable for use in office or clinic.

FIG. 1. Shoulder-hand syndrome involving the left hand.

REPORT OF CASES

Case 1.—A 67 year old retired businessman had been known to have hypertension for several years. Three months before hospital admission he noted sudden onset of weakness of the left arm and leg and some difficulty in speaking. He was kept in bed at home for ten days, with resulting restoration of function of the arm and leg but a slight residual impairment of speech. Four or five weeks thereafter he noted stiffness and pain in the left shoulder and stiffness, swelling, and disability of the left hand and fingers, increasing in severity until hospitalization six weeks later.

Admission examination showed the heart to be regular in rate with no murmurs, but it was enlarged to the left. The lungs were clear. The blood pressure was 240 systolic, 120 diastolic. The neurologic examination revealed a slight left facial weakness. The pupils were equal and reacted well. There was some thickness of speech. The deep reflexes were slightly increased on the left and there was a questionable left Babinski. There was limitation of abduction of the arm at the shoulder to about 45 degrees. The patient was unable to touch his face with his left hand. The left hand and fingers were generally swollen with a brawny type of edema and exhibited a bluish red discoloration, more pronounced in dependency. The fingers were almost rigid and could not be flexed with passive motion to more than 30 degrees. There was no voluntary motion (figure 1). There was some limitation of motion at the elbow joint. The skin temperature was moderately increased over the left hand and wrist. Laboratory examinations revealed a normal blood count and urinalysis, and a negative Hinton reaction. An electrocardiogram showed left ventricular hypertrophy. X-rays of the left hand showed a moderate degree of decalcification involving the interphalangeal joints and the carpal region.

On the third hospital day a left stellate ganglion procaine block was performed and a Horner's syndrome resulted. Increased mobility of the shoulder joint was noted. The next day another block was done, following which he was able to put his left hand behind his head; there was increased flexibility of the fingers to passive motion and decrease of edema of the hand. The next day a third stellate block was carried out, and it was noted that the edema and discoloration of the hand and fingers were less prominent and the fingers could be bent passively to touch the palm without much discomfort. The patient stated that his shoulder joint felt much more mobile. He received four more stellate blocks over the course of the next 11 days, and on discharge the left hand was the same color as the right and the edema of the hands and fingers was much diminished. The fingers were more flexible, but he was still unable to clench his fist completely. There was greatly increased mobility of the shoulder joint and almost complete absence of pain. When seen one month later, he was able to raise the left arm almost vertically over his head. The swelling had disappeared and, although still unable to make a complete fist, the hand was functional for most purposes.

Case 2.—A 68 year old merchant stated that six months previously he had suddenly fallen to the ground, lost the use of his right arm, and noted difficulty in speaking. He was hospitalized for three weeks and recovered the use of his arm and most of his speech ability before discharge. Soon after this he noted onset of pain, some limitation of motion of the left shoulder, and

some aching of the right shoulder, but no interference with motion. The hands were not involved. These symptoms persisted with considerable discomfort in the left shoulder.

Examination showed limitation of abduction of the left arm at the shoulder to about 70 degrees. The patient was unable to put on his coat without assistance because of pain. There was some pain on motion of the right shoulder but no limitation of motion. Examination of the hands revealed no abnormality.

A left stellate ganglion block was carried out, followed by some relief of pain on motion of both shoulders. Two more blocks were done on the left over a period of six days, with almost complete relief of pain and a greater range of motion in the left shoulder. He was able to put on his coat by himself without discomfort. Six months later he stated that he had no further shoulder pain but had noted a slight residual stiffness of the left shoulder. He was able to elevate his left arm over his head but could not achieve a completely vertical position. Four months later pain and stiffness in both shoulders recurred.

Case 3.—A 61 year old mechanic was admitted to the hospital on March 8, 1951, because of sudden onset of weakness of the left side of the body. There had been a previous history of hypertension. On examination he was mentally alert but unable to speak clearly. The blood pressure was 170 systolic, 110 diastolic. The neurologic examination revealed left facial weakness and hemiparesis involving the left side. He was unable to touch his face with his left hand or to raise the left leg from the bed. The deep reflexes were increased on the left. A lumbar puncture showed an initial pressure of 310 mm.; the cerebrospinal fluid was clear and colorless with a total protein of 54.58 mg. per cent. The blood and spinal fluid Hinton tests were negative.

The patient was treated with a series of contralateral stellate ganglion blocks over the course of the next 18 days. There was a recovery of function of about 80 to 85 per cent, and he was discharged on the twenty-eighth hospital day. At this time he was able to walk unassisted, raise his left arm over his head, and clench the fist. There was still residual left facial weakness.

Eight days after discharge he noted onset of pain and stiffness in the left shoulder and hand. The pain became very severe, especially in the shoulder, and kept him awake at night. The examination revealed disability and pain on motion of the left shoulder, with abduction limited to 60 degrees. There was stiffness and pain on motion of the fingers, with slight swelling and erythema. The symptoms became gradually worse, and a series of three left stellate ganglion procaine blocks was performed over a period of eight days. Immediate relief of pain and increased mobility in the hand and shoulder were noted after each block. When seen on May 16, 1951, there was some residual stiffness of the left shoulder and fingers but no pain. On June 18, 1951, he reported recurrence of left shoulder pain at night and stiffness of the fingers. A left stellate ganglion block was performed and increased finger mobility and relief of pain were noted immediately. He returned to work. He was seen again on July 7, 1951, and complained of stiffness of the left hand and fingers. He received another left stellate ganglion block and increased flexibility of the fingers was noted. He was not seen again until October 5, 1951, when he reported further no difficulty with his hand and shoulder. He was able to perform his work as a mechanic, involving fine movements of the fingers.

SUMMARY AND CONCLUSIONS

1. The shoulder hand syndrome frequently occurs as a complication following cerebral vascular accidents. The manifestations may be mild and of short duration or may progress to severe pain, disability, and trophic changes.

2. Homolateral stellate ganglion procaine block affords relief of pain and improvement in disability in most cases.

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Neurology BOOK REVIEWS

Epilepsy and the Functional Anatomy of the Human Brain.

Wilder Penfield, M.D., D.Sc., F.R.C.S., F.R.S., and Herbert Jasper, M.D., Ph.D., D. es Sci., with a chapter by Francis McNaughton, M.D. 1954. Boston: Little, Brown and Company. 896 pages. 322 illustrations. $16.00.

Neurologists are not only familiar with but constantly use as a reference the book, *Epilepsy and Cerebral Localization*, written by Drs. Wilder Penfield and Theodore C. Erickson in 1941. Two later monographs by Dr. Penfield, *The Cerebral Cortex of Man* (written with Dr. Theodore Rasmussen and published in 1950) and *Epileptic Seizures Patterns* (written with Dr. Kristian Kristiansen and published in 1951), have been added to his voluminous literature and have aided neurologists, neurosurgeons, electroencephalographers in their attempt to keep abreast of the advances that are being made in the studies of cortical localization and epilepsy, and especially of those investigations that have been carried out at the Montreal Neurological Institute. This new book, the reader is told, is a sequel to, or possibly a revised edition completely rewritten with a change of joint authorship, of the Penfield-Erickson volume.

It is difficult to know just how to review this book, other than to state that it is a complete summary of the investigations of the two authors brought up to date. Their conclusions are based on their extensive clinical experience, in which every patient has been studied in detail. The purpose of the volume, according to the authors, was "to achieve a better understanding of the mechanisms and causes of epileptic seizures so as to provide a more rational and more effective treatment for patients who are subject to various forms of cerebral seizures. This has led to the secondary, but ever more engrossing, consideration: the functional anatomy and physiology of the human brain. Any epileptic patient whose case has been completely studied may well provide a dramatic demonstration of functional localization in the cerebral cortex during the evolution of his attacks."

An interesting and valuable feature of the book is the signing of each chapter by the author who wrote it, rather than assigning the entire volume to joint authorship. Dr. Penfield's chapters review and bring up to date his well known classification of the epilepsies, his work on cerebral localization and epileptic mechanisms, his descriptions of the various focal cerebral seizure patterns, and his accomplishments in the surgical removal of epileptogenic lesions. An outstanding advance over the Penfield-Erickson volume, to which Dr. Jasper had contributed an important but small section, are Dr. Jasper's chapters on electrophysiology, electroencephalography, electrocorticography, experimental epilepsy, and subcortical relationships. As

anyone familiar with their work might expect, the chapter on "centrencephalic or highest level seizures" was written jointly. Dr. Jasper's historical introduction is an interesting and valuable preface to the book, and Dr. McNaughton's chapter on medical therapy reviews the general aspects of nonsurgical treatment.

This comprehensive study is an outstanding contribution to both the understanding of epilepsy and the clinical applications of our knowledge of the structure and functions of the cerebral cortex. Clinical neurology owes a great debt to Drs. Penfield and Jasper – not only for the scientific advances they have made, but also for this volume in which they have correlated their work and presented it in a clear and concise manner. It is indeed a tribute to John Hughlings Jackson and Sir Charles Sherrington, to whom it is dedicated.

R. N. DE J.

The Management of Pain.
With Special Emphasis on the Use of Analgesic Block in Diagnosis, Prognosis, and Therapy.

John J. Bonica, M.D. 1953. Philadelphia: Lea and Febiger. 1533 pages. 785 illustrations. $20.00.

This book is a comprehensive study of the general subject of pain, the various diseases and disorders in which pain constitutes a major problem, and the methods employed in its management, with special emphasis on the use of analgesic block as an aid in diagnosis, prognosis, and therapy. The book is composed of three parts. The first is a discussion of the fundamental aspects of pain, including the anatomic, physiologic, and psychologic bases as well as the mental and physical aspects of pain. The second deals with the methods and technics of managing pain, not only by analgesic block but also by drugs, psychotherapy, physical therapy, orthopedic methods, roentgen therapy, and neurosurgical approaches. In the third part are presented various painful syndromes and their diagnosis and management. These are grouped as follows: neuritis and neuralgia; causalgia and other reflex dystrophies; pain consequent to vascular disease; pain of somatic origin (muscles, joints, bone, skin); pain of visceral origin; pain of cancer and allied diseases.

This book is certainly an ambitious endeavor and is almost encyclopedic in its scope. It was written by an anesthesiologist, and should be of major interest to those in the author's field. It should also, however, be a valuable reference volume to the neurologist. While the latter may take issue with certain of the anatomic and physiologic concepts as well as with some of the clinical descriptions, many of the fundamental considerations as well as the general principles of diagnosis and management of the patient are very well presented and adequately illustrated. Some of the chapters are written by collaborators, who are identified only at the chapter headings. Dr. Herbert S. Ripley has contributed short but adequate discussions of the psychologic basis of pain and psychotherapeutic methods in the management of pain. Dr. John T. Robson's chapter on neurosurgical methods is certainly brief, in contrast with the lengthy discussions of other methods, and he gives only cursory – and far from favorable – presentations of such methods as chordotomy, tractotomy, and prefrontal lobotomy.

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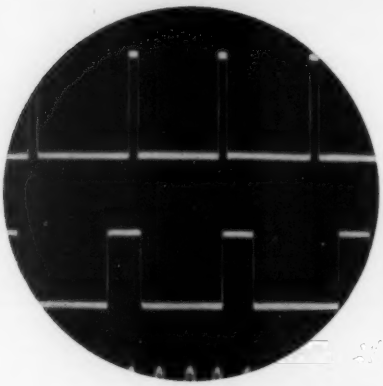

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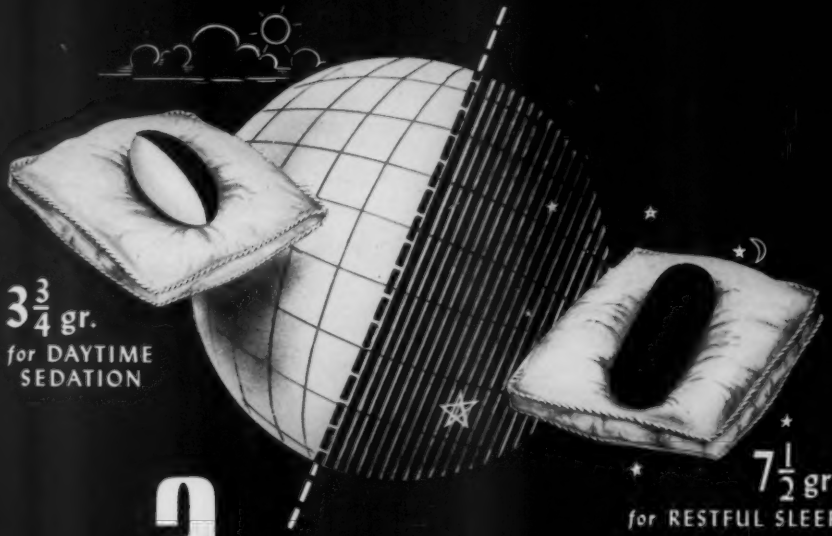

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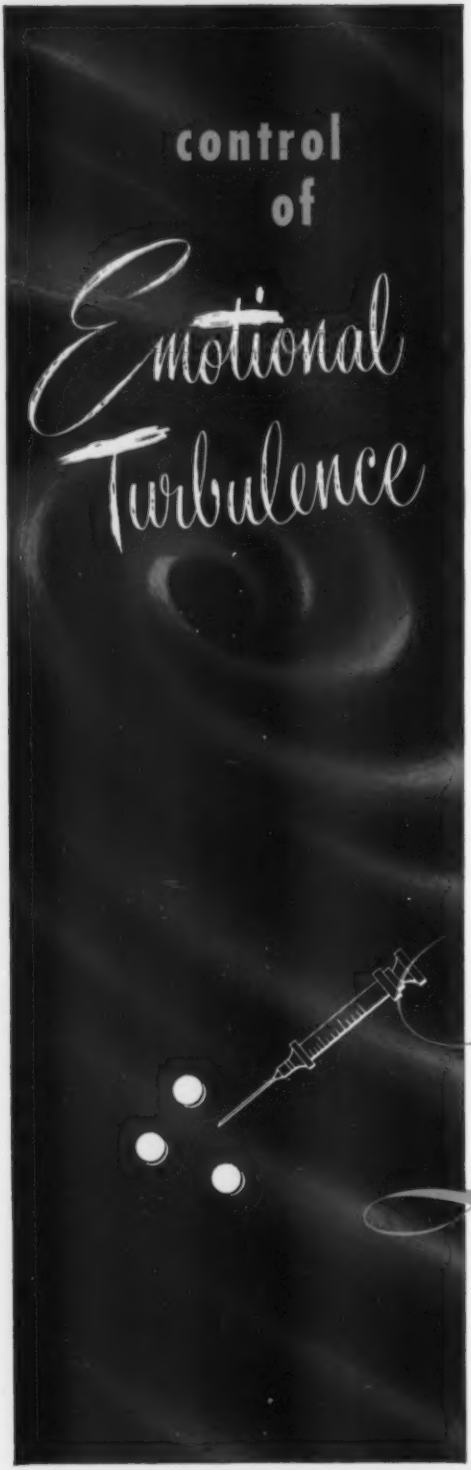

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